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OPENING ADDRESS

This symposium is devoted to hypertension a field in medicine in which over the last two decades much progress has been made on both the epidemiologic and the therapeutic levels. Due to its high prevalence and its serious socio-economic implications hypertension has been recognised as a major community health problem for which the solution lies to a great extent in early diagnosis and subsequently adequate treatment

Although, I am speaking for a pharmaceutical firm, which with its past and present research activities, is heavily engaged in the search for and development of new antihypertensive agents, I do by no means pretend that drug therapy is the only possible approach to the problem A more healthy way of life with less exposure to stress, with reduced food consumption and diminished salt intake would certainly make a very important contribution but I feel quite safe in saying that at the present time and for the next few years—may be even decades—drug therapy will continue to have a better chance of reducing the problem of hypertension than any attempt to alter communities living habits.

This is even more the case since the use of modern antihypertensive drugs—and I am referring here mainly to the β-adrenoceptor blocking agents—can be based on a very much improved understanding of the underlying pathophysiological and in particular haemodynamic principles of hypertension, and cause much less discomfort to patients than the older drugs.

Since I was a pharmacologist in my earlier years, I am still intrigued by the question of whether and to what extent results obtained in animals can be applied to man There is growing evidence that in man early and proper antihypertensive therapy reduces the risk of stroke cardiac and renal insufficiency and possibly also of myocardial infarction thereby prolonging the period of enjoyable life and lowering mortality of the disease In this context I would like to show very briefly two figures which illustrate results obtained by Dr Salzmann from our Pharmacology Department on the effects of early treatment of experimentally induced hypertension in rats.

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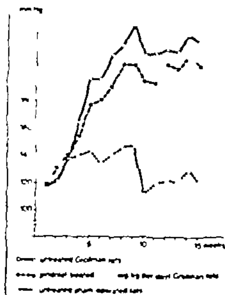
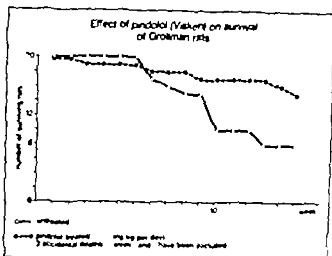


Fig 1



Fig

Figure 1 shows the development of blood pressure in untreated and pindolol treated Grollman rats and in sham-operated untreated animals The drug was given in a daily dose of 0 5 mg/kg in the food from the time when the first surgical procedure on one kidney was performed until the end of the 15th week after surgery Compared with the results from other animal models for instance the spontaneously hypertensive rat or DOCA and salt induced hypertension the reduction in blood pressure achieved by pindolol in the Grollman rat was not very impressive and in most measurements not statistically different from non treated controls.

However as shown in Figure 2 the small differences may have been of some therapeutic significance. Here the number of surviving animals is plotted against time. Clearly β receptor blockade resulted in an improved survival rate and it is of course tempting to speculate that this protection was at least partially due to the modest reduction in arterial blood pressure

It would be of interest to go into more details of this and similar studies and to discuss the predictability of animal experiments for the human use of antihypertensive drugs. However this is not the topic of todays discussion and I would therefore like to conclude by thanking all of you for having accepted the invitation to come to Basle and by expressing our sincere gratitude to the four chairmen and all the speakers for their willingness to actively participate in our symposium

Konrad Saameli MD
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The Care of the Hypertensive Patient

Chairman Gösta Tibblin

Department of Social Medicine University of Umeå Umeå, Sweden



Fig 1

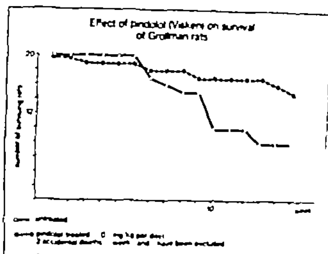


Fig 2

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Treatment of Hypertension in the Community

A preliminary report

Goran Berglund, Ove Anderson and Lars Wilhelmsen

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Abstract. The feasibility and efficacy of antihypertensive treatment within the Primary Prevention Trial against myocardial infarction and stroke in Göteborg, Sweden, are described. The study group consisted of 9 967 men aged 47—54 years, chosen at random from the general population. 75% of them participated in a screening examination including a blood pressure (BP) measurement. Hypertension defined as BP above 175 mm Hg systolic or 115 mm Hg diastolic on two separate occasions or antihypertensive treatment was found in 9%.

The drop-out rate was 6.5% during the first year and 3.6% during the second year of treatment. The percentage of hypertensive subjects with uncontrolled BP decreased from 83% at screening to 16% after one year and to 9% after two years of treatment. The frequency of side-effects of such severity as to cause withdrawal of drugs, was 16% during the first year and 7% during the second year.

The morbidity in coronary heart disease and stroke in those hypertensives (n=696) treated at the Hypertension Clinic was compared with that of an untreated control group (n=330). The incidence of death and fatal plus non-fatal myocardial infarction was significantly lower in the treated group than in the untreated comparison group in spite of lower initially predicted risk of myocardial infarction in the comparison group. The findings indicate that antihypertensive treatment prevent the occurrence of coronary heart disease.

In selected groups of hypertensive subjects (15, 16) antihypertensive treatment has been shown to prevent the development of stroke and other diseases directly related to increased blood pressure (BP). These studies were unable, however, to show an effect of treatment on the incidence of coronary heart disease. Furthermore, the feasibility of keeping large populations under treatment for long periods of time with low drop-out and side effect rates and with acceptable BP control has been questioned (1).

This paper presents the feasibility and efficacy of antihypertensive treatment at a specialized Hypertension Clinic in an unselected male middle aged Swedish population.

STUDY POPULATION AND METHODS

The present study population was recruited from a screening examination which was part of a primary preventive trial started in 1970 (18). Pertinent data on the study population and trial design are given in Figure 1. Details of the screening examination as well as the BP criteria for further action, such as diagnostic investigation and treatment, have been described previously (19). Briefly

The Primary Preventive Trial, Göteborg, Sweden

Main objective: Intervention

End-points for evaluation: Mortality, total and cause specific
Morbidity from CHD and stroke

Duration of the study: ca. 1970–[illegible]

Study group: General population 10 000 M 47–54 years

Control group: General population 20 000 M 47–54 years

Definition of HT: >175 and/or 115, 2 measurements, or treatment

Case finding made by non-communal specialized clinic

Treatment: *Study group:* No standardized protocol
Control group: No case finding done

Treatment prescribed by specialized clinic

Educational measures directed towards HT-pertensive subjects

Fig. 1. Data on study population and methods. CHD = Coronary heart disease. HT = Hypertension.

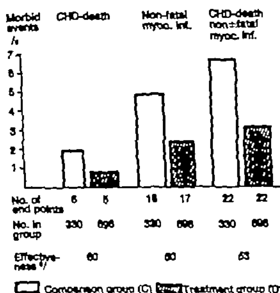


Fig. 4 The percentage incidence of death from coronary heart disease and non-fatal myocardial infarction in the Comparison group (C) and the Treatment group (D)

Table 1 The drop-out rate during the first and second year of treatment at the Hypertension Clinic.
The Primary Preventive Trial, Göteborg, Sweden
(n=696)

	1st year n	% of 696	2nd year n	% of 696
Remaining under control (the Hypertension Clinic	646	94.2	624	91.0
Drop-outs	40	5.8	22	3.2
Refused	5		2	
Defaulted	17		8	
Moved	7		4	
Died	6		5	
Other reasons	5		3	

Table 2. The frequency of good acceptable and poor blood pressure control after one and two years of treatment at the Hypertension Clinic.
The Primary Preventive Trial, Göteborg, Sweden
(n=696).

	1st year	%	2nd year n	%
Treated	610		589	
BP-control				
<160 and 95 mm Hg	199	33	262	44
160—175 or 95—115 mm Hg	31.	51	776	47
>175 or 115 mm Hg	99	16	51	9

The drop-out rate

During the first year 5.8% and during the second year 3.2% dropped out of treatment (Table 1). These figures include drop-outs due to death and migration (2.0% during the first year and 1.3% during the second year).

The BP control

At the screening examination 83% of the hypertensive subjects had BP above the limits for hypertension (Figure 3). The corresponding figures after one and two years of treatment were 16% and 9% (Table 2). Only 33% and 44% respectively had definitely normal BP i.e. below 160 mm Hg systolic and 95 mm Hg diastolic.

Side-effects causing withdrawal.

During the first year 16% and during the second year 7% experienced side-effects of such severity as to cause withdrawal of the drug and institution of alternative therapy (Table 3). In the great majority of cases the reported side-effects could not be attributed to drug-specific effects.

Effects of the treatment on cardiovascular events.

Twenty-two of the 696 hypertensive men (3.2%) treated and followed up at the Hypertension Clinic had a fatal or a non-fatal myocardial infarction during the follow-up period (Figure 4). The corresponding figure in the untreated comparison group was 22/330 (6.7%). The difference was statistically significant ($p<0.05$). When fatal plus non-fatal strokes were added ("all cardiovascular events") there was still a statistically significant difference ($p<0.05$).

There was a significant difference in total mortality ($p<0.05$) while no significant difference was found for mortality from coronary heart disease or stroke between the hypertensive subjects treated at the Hypertension Clinic and the untreated control group.

Table 3 The frequency of side-effects of such severity as to cause withdrawal of the drug. Results are given separately for the first and second year of treatment.
The Primary Preventive Trial, Göteborg, Sweden
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	1st year n	%	2nd year n	%
On treatment	610		589	
Withdrawal due to side-effects	98	16	38	7

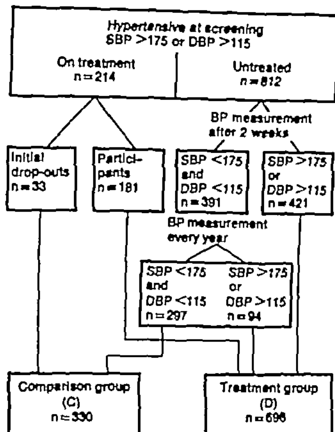


Fig Creation of a Comparison group (C) and a Treatment group (D)

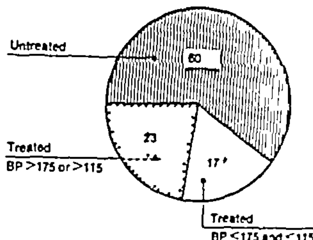


Fig 3 The prevalence of hypertension and the proportion of treated and untreated hypertensive subject

of the 9 967 47—54 year-old men invited to attend 75% took part in a screening examination. Those with BP above 175 mm Hg systolic or 115 mm Hg diastolic on two separate occasions and those on antihypertensive treatment (n=686) were subjected to a standardized diagnostic investigation (19) Those with BP above the limits for hypertension at screening but not at the BP check up two weeks later were recalled for another BP check-up after one year The criteria for referal for treatment are given in Figure 2. This figure also shows how a treated and an untreated group were created for the comparison of mortality and morbidity It is worth noting the difference in composition between the group of 696 men according to Figure 2 and the group of 686 men described in Figure 3 The treatment group in Figure 2 includes the subgroup of 94 men who were found to be hypertensive at yearly BP-checkups, while the latter is a group of well treated hypertensives (SBP <175 and DBP <115)

After the diagnostic investigation at the Hypertension Clinic the hypertensive subjects were put on hypotensive treatment Although the treatment policy has not been rigorously uniform from 1970 until 1976 treatment has been started with a beta blocker in the great majority of patients adding a saluretic diuretic or hydrallazine or both if normotension has not been achieved The clinic was responsible for giving appointments to the patients and those who failed to attend an appointment were actively sought out in order to return them for further follow-up

Non fatal and fatal myocardial infarctions and strokes, and all deaths including sudden deaths, were followed by means of registers covering all cases in Göteborg (7 9) The morbidity analysis covers a follow-up period from the start of the study in 1970 until December 31st 1975

Statistical methods used included Chi squared test for comparison of proportions and Student's t-test for comparison of mean values A multiple risk factor was assigned to the subjects with the aid of a computer according to a multiple logistic function described previously (20)

RESULTS

Prevalence of hypertension

Hypertension defined as BP above 175 mm Hg systolic or 115 mm Hg diastolic on two separate occasions or current antihypertensive treatment was found in 686 men (9%) Of these 60% were untreated and 23% were treated but had BP above the cut off points for hypertension Only 17% had an acceptable BP control i e BP below 175 mm Hg systolic and 115 mm Hg diastolic (Figure 3)

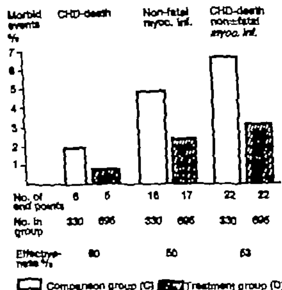


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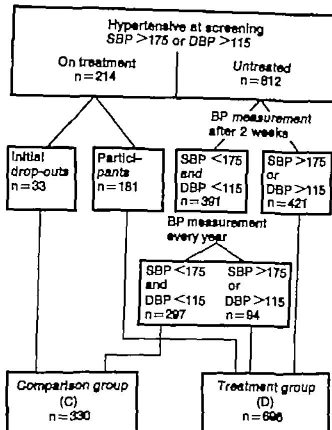


Fig 2 Creation of a Comparison group (C) and a Treatment group (D)

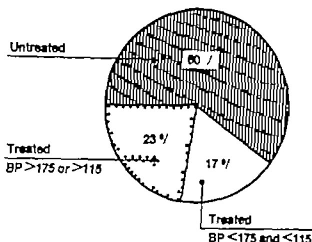


Fig 3 The prevalence of hypertension and the proportion of treated and untreated hypertensive subjects.

of the 9 967 47—54 year-old men invited to attend 75% took part in a screening examination. Those with BP above 175 mm Hg systolic or 115 mm Hg diastolic on two separate occasions and those on antihypertensive treatment (n=686) were subjected to a standardized diagnostic investigation (19) Those with BP above the limits for hypertension at screening but not at the BP check up two weeks later were recalled for another BP check-up after one year The criteria for referal for treatment are given in Figure 2. This figure also shows how a treated and an untreated group were created for the comparison of mortality and morbidity It is worth noting the difference in composition between the group of 696 men according to Figure 2 and the group of 686 men described in Figure 3 The treatment group in Figure 2 includes the subgroup of 94 men who were found to be hypertensive at yearly BP-checkups, while the latter is a group of well-treated hypertensives (SBP < 175 and DBP < 115).

After the diagnostic investigation at the Hypertension Clinic the hypertensive subjects were put on hypotensive treatment. Although the treatment policy has not been rigorously uniform from 1970 until 1976, treatment has been started with a beta blocker in the great majority of patients, adding a saluretic diuretic or hydralazine or both if normotension has not been achieved. The clinic was responsible for giving appointments to the patients and those who failed to attend an appointment were actively sought out in order to return them for further follow-up

Non-fatal and fatal myocardial infarctions and strokes, and all deaths including sudden deaths, were followed by means of registers covering all cases in Göteborg (7 9). The morbidity analysis covers a follow-up period from the start of the study in 1970 until December 31st, 1975

Statistical methods used included Chi-squared test for comparison of proportions and Student's t-test for comparison of mean values. A multiple risk factor was assigned to the subjects with the aid of a computer according to a multiple logistic function described previously (20)

RESULTS

Prevalence of hypertension

Hypertension defined as BP above 175 mm Hg systolic or 115 mm Hg diastolic on two separate occasions or current antihypertensive treatment was found in 686 men (9%) Of these 60% were untreated and 23% were treated but had BP above the cut off-points for hypertension Only 17% had an acceptable BP control i e BP below 175 mm Hg systolic and 115 mm Hg diastolic (Figure 3)

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12. Miall, W E., The MRC trial for mild hypertension. WHO/ISH Meeting of Investigators. CVD/H/75 4

13 Tibblin, G High blood pressure in men aged 50-population study of men born in 1913 Acta med Scand Suppl. 470 1967

14 Tuomilehto, J Puska P & Rimpelo M. Hypertension epidemiology Nordkarelen, Finland. In Hypertension—Nordiskt symposium i Göteborg 1973 (ed. A Vedin C Wilhelmsson & L. Werko) Lundgren & Söner AV p 129 Göteborg 1973 (English summary)

15 Veterans Administration Co-operative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. J Amer Med. Assoc 202 1028, 1967

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18 Wilhelmsen, L., Tibblin, G & Werkö, L A primary preventive study in Göteborg, Sweden. Prev Med 1 153 1972

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The blood pressure observation was made with the patients in a recumbent position without rest during daytime. One single observer made the screening and she had been tested with several other observers as to the reliability of the readings and did not differ from the rest of the group. She had a detailed description and used a mercury manometer The balloon in the cuff was 12×35 cm. The readings were made per 2 mm and the diastolic pressure read in phase 5

The population studied was completely unselected and comprised everyone over 25 years of age, that is 2626 men and 2745 women. 87 per cent of the men and 85 per cent of the women were examined. In certain age groups the participation rate was more than 90 per cent.

The criteria for selection were unknown to the nurse who made the screening. The limits had been set ery low in order to give the opportunity to make a thorough evaluation of hypertensives in the area.

The result of the screening was unexpectedly low 4 4 per cent of the men and 2,8 per cent of the women. In total 166 persons had abnormal screening findings. Among these there were 53 known hypertensives. Of the remaining 113 only 34 fulfilled the criteria for therapy hich, in the scheduled programme were put at more than 105 mm mercury diastolic and, for patients over 60 years of age, more than 110 mm. (Mean of three separate readings, the screening excluded). After carefully going through all the papers at the out

No difference in age cholesterol or smoking habits at entry was found between the treated group and the untreated comparison group

DISCUSSION

We have chosen to study men within a narrow age span in order to minimize any influences of age and sex on the variables studied. The study population has been drawn so that the results can be applied to other male populations with a similar background This is acceptable if the non participation group doses not differ substantially from the population studied Earlier epidemiological studies by our group have shown that the non participation group may differ in respect of socioeconomic factors (13) and mortality (?0) The non-participation rate in the present study was 25% Similar or even higher rates have been reported in certain other population studies (3 5 6 8) Other studies, however have shown higher participation rates (11 13 14) The present study which is a primary preventive trial was designed so that it would be possible to repeat it on a larger scale if the results proved favourable. Further efforts have therefore not been made to get hold of those who did not answer two letters of invitation. It has been supposed that those who were unwilling to attend a screening examination would also be reluctant to comply with treatment regimens.

The limits for hypertension (175/115 mm Hg in the afternoon) may appear to be high. Results of BP measurements in the morning (16?/101) (19) the distribution of patients by WHO stage and findings concerning cardiac (17) and renal function (2) all indicate however that most hypertensives studied had mild to moderate hypertension without serious heart or kidney damage at entry

The descriptive BP data are in good agreement with earlier studies in Göteborg (19) and elsewhere (10) showing that a majority of persons with hypertension were untreated and that a large proportion of those on treatment had high BP

The programme for control of hypertension proved to be effective in lowering BP in the majority of hypertensives. However there still remained a substantial proportion of patients whose BP could not be adequately controlled despite heavy antihypertensive drug therapy Obviously there is a great need for further knowledge of the cause of the poor BP response in this group. More potent antihypertensive drugs are also needed. The BP decrease was achieved with an acceptable frequency of side-effects, the drug withdrawal rate due to side-effects being fully comparable with that in another large-scale hypertension study (1?) The drop-out rate was extremely low compared to conventional management (1 4).

The results regarding the incidence of cardiovascular events indicate a preventive effect of the programme on the occurrence of coronary heart disease One must remember however that this is not a strict double blind trial with a treatment group and placebo-treated control group It is therefore not possible to ascribe the preventive effect solely to the drug regimen used as benefical effects from the closer supervision of the treated group cannot be ruled out. Further evaluations will disclose whether this was the case The difference found cannot be explained by different risk patterns in the two groups as no differences were found in the usual risk factors for coronary heart disease.

This study shows that BP treatment, in the hands of specialists, is feasible and that it also seems to be effective in reducing the morbidity from cardiovascular diseases.

REFERENCES

1 Adler M. V d'Souza M. F & Holland, W W The drop-out problem and the effectiveness of population treatment of raised blood pressure In Pathophysiology and Management of Arterial Hypertension (ed. O Berglund L Hansson & L Werkö). Lindgren & Soner p ?75 Molndal 1975

2 Berglund G Aurell M & Wilhelmsen, L Renal function in normo- and hypertensive 50-year old males. Acta med Scand 199 25 1976

3 Bøe J Humerfelt S. & Wedervang F The blood pressure in a population Acta med Scand Suppl. 321 1957

4 Caldwell J R Cobb S Dowling, M D & de Jong D The drop-out problem in antihypertensive treatment J chron Di 22 579 1970

5 Comstock G W An epidemiological study of blood pressure level in a biracial community in the Southern United States Amer J Hlg 65 ?71 1957

6 Dawber T R Meadors G F & Moore F E Jr Epidemiological approaches to heart disease Framingham study Amer J publ Hlth 41 ?79 1951

7 Elmfeldt, D Wilhelmsen, L., Tibblin, G Vedin, A., Wilhelmsson C. & Bengtsson C. Registration of myocardial infarction in the city of Göteborg, Sweden. J chron. Dis 28, 173, 1975

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patient clinic, 480 hypertensives were found who had received therapy before the screening.

However the criteria for the diagnoses hyper tension and for therapy among these were probably not exactly the same as the above mentioned but they are considered hypertensives in this study

That gives a figure of 10 per cent hyperten sives in the population over 25 years of age.

The diastolic pressures for men age 50—54 have been compared with some other wellknown studies but there are at present no comments as to the differences.

Special interest has been paid to the non parti cipating group. As expected the youngest and the oldest are in majority here. Of 764 or 14 per cent of the studied population that did not participate in screening it has been possible to get informa tion on blood pressure for 533 That means that it has been possible to estimate the prevalence of hypertension for 96 per cent of the studied popu lation.

The following conclusions have been drawn

1 A well run outpatient care organization in Sweden in this case one doctor per 3500 inhabitants, is able to detect, take care of and treat all the hypertensives in the population from the quan titative point of view

2. With a strictly scheduled programme with fixed criterias for therapy therapy goals, schedul ed routines for examination and check ups, and with the possibility of delegating certain tasks to a nurse it is possible to cover patients with other diagnosis as well

3 A screening procedure gives very poor results where outpatient care is well established and is probably only of value initially

Bengt Schersten
I have a question to Göran Berglund How was the blood pressure measured? During screening it was measured in the sitting position I think. How was it measured during the control?

Göran Berglund
During the controls it was measured after five minutes rest in the sitting position At the screen ing the rest was 3—5 minutes, during which time an interview was carried out Thus they are quite comparable.

John-Fredrik Dymling
Did you make any attempt to compare the morbidity of the groups, which did not have well controlled hypertension? There were quite a few people in these groups.

Göran Berglund
The end point numbers are still fairly small In the treated group and in the comparison group only about 20 up till now had a myocardial in farction Further subdivision into those who had normalised blood pressure and those who still ha high blood pressure would make a statistical ana lysis impossible.

Johan Asplund
How many of your patients in the treated group were on beta blockers?

Göran Berglund
Beta-blockers are the first choice drugs at our clinic. About 75% of the patients are on a beta-blocker now

Lennart Sölvell
The frequency of side-effects was about 25% in two years. Could you tell us anything about the type of side-effects?

Göran Berglund
We had about the same frequency of side-effects in the saluretic treated patients and in the beta blocker treated patients. The usual cause of withdrawal in the saluretic group was hypokalemia, in spite of a heavy potassium supplement. In some patients gout also occurred. In the beta-blocker group there were more unspecific types of side-effects. It was very hard to say if they were drug related or not In one or two cases we found a heart decompensation

Gösta Tibblin
As you said this is neither a double blind study and nor a controlled randomised study What kind of differences could exist between the two groups, the control group and the experimental group? Perhaps the control group has a more variable blood pressure? We know from our own study that a large variability in the pressure can be a risk factor in itself The other question is whether there are any differences in smoking habits, in cholesterol and so on between the two groups?

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We have not yet finished the rescreening of the whole group. That will be done in 1977 However it is quite clear that there is a more variable blood pressure in the control group The treatment group must have had a more stable blood pressure since the criterion was two blood pressure measure ments of 175/115 or more It is possible that a variable blood pressure is a more pronounced risk factor than a stable blood pressure We cannot answer that question

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It has been stressed repeatedly that our medic l care resources are not large enough to allow proper treatment of hypertension in the popula tion. The results of the Edsbyn tudy imply that the situation may not be bad and that a large

proportion of the Swedish population may already have proper antihypertensive care.

Sven-Olof Isacsson
I can agree with Sören Jakobsson to some extent, but overall our experience in Skaraborg county is that we have about the same proportion of treated cases as you have in Gothenburg. In most communities we have around 15% on adequate treatment and the rest are not treated or on inadequate treatment.

Göran Berglund
Did you have a physician in Edsbyn, who was particularly conscientious and who had been established for many years, which could explain the low frequency of unknown hypertensives?

Lars Sundman
Maybe this was a factor but it is by no means clear. The physician had been working in Edsbyn for only two years when we started. We are going to carry out a similar study in another part of our county to see what situation we have there.

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I think it is very important to realize that Edsbyn is certainly not representative for primary medical care in the whole of Sweden. In the north, we are still short of doctors, and can certainly not deliver such good primary medical care.

Bernt Hokfelt
Would you care to comment on the prevalence of hypertension in a city as compared to a rural district?

Lars Sundman
I cannot answer your question specifically but it is our impression, that blood pressure levels in the Edsbyn region are lower than those in the city of Gavle. However I have no comments at all as to why this is so.

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Long-term Aspects on Essential Hypertension

Ingvar Liljefors

F om the Department of Internal Medicine St Göran Hospital Stockholm Sweden

Abstract. Hypertension has been found to imply a disease entity since the beginning of this century Effective treatment available in the last two decades has changed the outlook remarkably especially in malignant hypertension.
There are more and more evidence that less severe forms of hypertension will benefit from keeping the blood pressure under control.

In 1913 Dr Theodore C Janeway (8) read a paper before the Association of American Physicians on a series of nearly 500 patients with hypertension seen in his private practice and followed for 9 years Based on this study he then made a statement which is still valuable.

It does not seem to me that any very definite prognostic conclusions can be drawn from the height of the blood pressure. This paradox has been evident to all physicians up to the present time when a high blood pressure is revealed

The existance of some patients with well defined diseases, such as nephritis, aortic valve insufficiency or thyreotoxicosis was well known. The majority of patients with hypertension did not, however present such etiology and thus the prognostic judgement had to be based on experience of different types of essential hypertension.

Based on the clinical studies of Volhard and Fahr (11), the three representatives of different branches of medicine Keith, Wagener & Barker (9) suggested that the prognosis of hypertensive patients would be ecognized by classification of the eye ground pattern Their study comprised a series of 219 patients followed for 7 years, and it displayed a quite different outlook for the 4 groups (Figure 1). Malignant hypertension with its urgent need for effective treatment, is probably still most clearly identified by recognizing the papilloedema

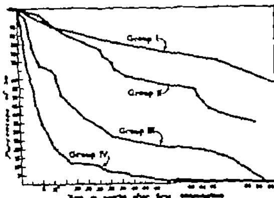


Fig 1 Survival curves in the four groups according to Keith, Wagener & Barker (1939).

of the group IV patients. At the same time when treatment of hypertension was restricted to combatting its effects on various organs, the outlook for the patients with the malignant type was very bad. The average time of survival was less than one year the main death cause being uraemia. This form of hypertension represents only a small part of the hypertensive population but is still a challenge to the therapeutic efforts. The prognostic value of Keith & Wageners classification groups I—III has been disputed The difficulty even for ophtalmic specialists, of classifying the eye ground pattern is well known. We also know that a benign hypertension may suddenly take a malignant course.

The prognosis of hypertensive disease as recorded in clinical series before the new era of hypertensive treatment, varied considerably depending on the criteria for inclusion of patients. Certain characteristics of importance for the future development of the disease have however been recognized. Here again I would like to quote Dr Janeway from 1913 "I have always had the impression that the expectancy of life of in women

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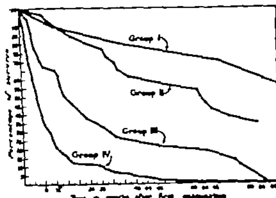


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**Abstract. Hypertension has been found to imply a disease entity since the beginning of this century Effective treatment available in the last two decades has changed the outlook remarkably especially in malignant hypertension.
There are more and more evidence that less severe forms of hypertension will benefit from keeping the blood pressure under control.**

In 1913 Dr Theodore C Janeway (8) read a paper before the Association of American Physicians on series of nearly 500 patients with hypertension seen in his private practice and followed for 9 years Based on this study he then made a statement which is still valuable.

It does not seem to me that any very definite prognostic conclusions can be drawn from the height of the blood pressure This paradox has been evident to all physicians up to the present time when a high blood pressure is revealed.

The existance of some patients with well defined diseases, such as nephritis, aortic valve insufficiency or thyreotoxicosis was well known. The majority of patients with hypertension did not, however present such aetiology and thus the prognostic judgement had to be based on experience of different types of essential hypertension.

Based on the clinical studies of Volhard and Fahr (11), the three representatives of different branches of medicine Keith, Wagener & Barker (9) suggested that the prognosis of hypertensive patients would be recognized by classification of the eye ground pattern. Their study comprised a series of 219 patients followed for 7 years, and it displayed quite different outlook for the 4 groups (Figure 1). Malignant hypertension, with its urgent need for effective treatment, is probably still most clearly identified by recognizing the papilloedema

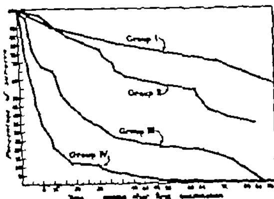


Fig. 1 Survival curves in the four groups according to Keith, Wagener & Barker (1939).

of the group IV patients. At the same time when treatment of hypertension was restricted to combatting its effects on various organs, the outlook for the patients with the malignant type was very bad. The average time of survival was less than one year the main death cause being uraemia. This form of hypertension represents only a small part of the hypertensive population but is still a challenge to the therapeutic efforts. The prognostic value of Keith & Wageners classification groups I—III has been disputed. The difficulty even for ophtalmic specialists, of classifying the eye ground pattern is well known. We also know that a benign hypertension may suddenly take a malignant course.

The prognosis of hypertensive disease, as recorded in clinical series before the new era of hypertensive treatment, varied considerably depending on the criteria for inclusion of patients. Certain characteristics of importance for the future development of the disease have, however been recognized. Here again I would like to quote Dr Janeway from 1913 "I have always had the impression that the expectancy of life of in women

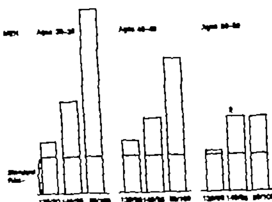


Fig. 3 Build & Blood Pressure Study (1959).

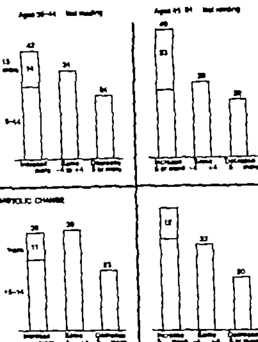


Fig. 4 Long-term changes in blood pressure of individuals; comparison of recent readings of male applicants with their readings taken at least 10—19 years previously (Build & Blood Pressure Study 1959).

that was revealed in this study namely "the increase with age does not mean a steady rise in blood pressure in every individual, but is the net effect of an increase in some individuals and relatively stationary level in others. As can be seen from Figure 4 less than half of the men and women in the middle age group increase their blood pressure substantially.

Introduction of potent drugs for the control of hypertension has offered a quite different prognosis of most significance to the patients with malignant hypertension. In Sweden we all know Bertil Hood as one of the most devoted advocates of the active treatment of malignant hypertension. Hood and his collaborators, at the beginning of the sixties, were able to present a material of 381 patients of whom 282 were adequately treated (2).

The survival rate of the 72 severe cases of Keith & Wagener grade IV is compared with less active treatment of the same grade of hypertension (Figure 5). There is no doubt that a great number of lives were saved using the new therapeutic possibilities.

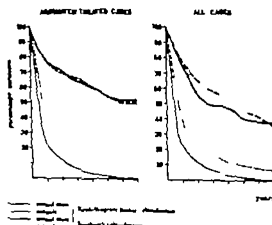


Fig. 5 Survival in treated cases of severe hypertension compared with controls (Björk et al. 1960).

In an attempt to evaluate active treatment of nonmalignant hypertension, Hamilton et al. (7) reported a controlled trial of 61 patients half of whom were given optimal treatment for blood pressure control.

	Age					
	30—39	40—49	50—59	60—69	70+	Total
Males	12.01	4 13	2.54	1.35	0.98	3 01
Females	6.21	5 10	1 91	1 12	0.80	1 62
All persons	7.51	4 91	2.22	1 15	0.87	1 85

Table 1 Observed/expected death rates in hypertension at different ages (corrected for length of follow up) based on 320 deaths in 669 untreated patients (Fry 1974).

FACTORS AFFECTING THE PROGNOSIS IN HYPERTENSION

FAVOURABLY	BADLY
Old parents	Heredity for CHD HT or diabetes
Female sex	Male sex
Age over 60	Age below 50 Black race
Hypertension known many years	Toxemia Renal disease Cerebrovascular disease
Variable blood pressure	Circulatory dysfunction Weight loss Known risk factors for CHD
Eye grounds I—II	Papilloedema Impaired renal function Cardiac enlargement

Table 2.

with arterial or renal disease was greater than in men Based on his long experience of over 1 000 cases of hypertension followed for about 40 years, Poul Bechgaard (1) has also pointed out the better outlook for female as apposed to male hypertensives.

An English practitioner Dr John Fry (6), reported in 1974 his experiences with hypertensive patients seen in general practice. Of about 700 patients with a diastolic blood pressure exceeding 100 mm Hg, half of which were less than 120 he followed 669 without treatment for 5 to 20 years. By comparing the death rates of the hypertensives with those of the general population in different age groups, he found the increased mortality to be restricted to the younger age groups especially for males (Table 1).

Apart from age and sex there are certain other factors of importance for the prognosis (Table 2). These factors should all be taken account of in deciding if and how a case of essential hypertension is to be taken care of

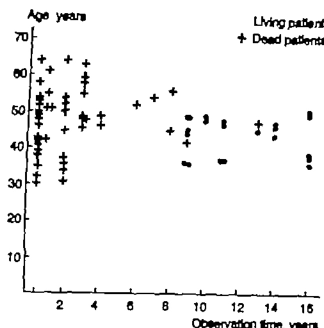


Fig 2 Follow-up of 83 hypertensive patients (Eliasch et al. 1970).

Another example of the prognostic variation in nonselected clinical material is Harald Eliasch follow-up study (5) of 83 hypertensive patients investigated around 1950 in St Erik s hospital in Stockholm. The majority of deaths occurred within 3 years of observation (Figure 2). The two main causes of death were cerebrovascular disease and cardiac insufficiency of which the former were dominated by women, and the latter by men. However the cardiac deaths were also associated with patients who were somewhat older at the beginning of the study

Clinical series of hypertensives are for natural reasons, highly selected from the general hypertensive population. Data on people with less severe hypertension is available from epidemiological studies and from insurance companies. One example of the latter is the Build and Blood Pressure Study (4) performed by the Metropolitan Life Insurance Company and based on 4 million people accepted for life insurance. The five times higher mortality compared with normals, for men between 30 and 40 with a quite discrete elevation of blood pressure is striking (Figure 3).

The Build and Blood Pressure Study also shows the wellknown fact that the mean blood pressure level increases with age. In this context, however I think it is well worth pointing out another fact

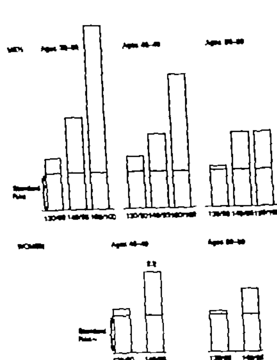


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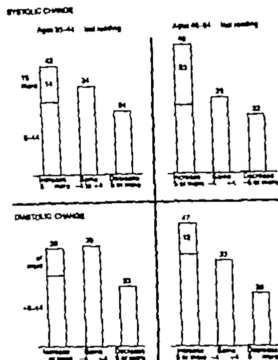


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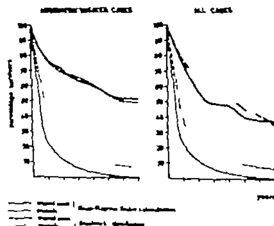


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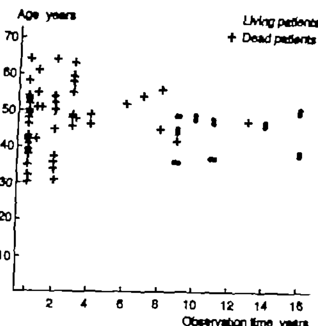


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Table 6. New England Life Mortality Experience 1954—1972 Borderline and definite hypertension Men, all Ages (Brown & Singer 1976).

Blood Pressure Category Mean	No. of Death Observed d	Claims Expected d'	Excess Death Rate 1000(d-d')/E	Mortality Ratio 100d/d'
Borderline 141/83	1,539	1,083.8	3.0	142%
Definite Systolic 163/89	112	68.2	5.6	164%
Definit Diastolic 147/100	107	67.5	3 7	159%
Definite S+D 170/103	161	80.4	8 0	200%

sure Study was performed and practically no effective hypotensive treatment was given.

A comparison was made between the two studies which had covered different time periods with different availability of therapy (Figure 6). The differences between the two studies in three of the blood pressure categories are significant at the 5 % level. These trends towards a decrease in the overall mortality may of course have several causes since many other factors have been altered to reduce mortality over the past twenty years. On practical, and by no means uninteresting factor resulting from the availability of new and less risky means of treating hypertension is the chance of keeping blood pressure and subsequently the insurance premium loading, under control

I will conclude with another quotation from Dr Janeway which is still suitable·

"This illustrates well the advantage of life insurance examination for the early detection of chronic disease

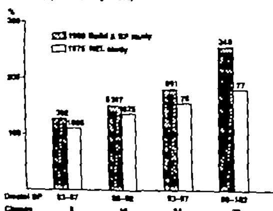


Fig 6 Comparison of mortality ratios by diastolic blood pressure category Men 40—49 (Brown & Singer 1976)

REFERENCES

1 Bechgaard, P The natural history of benign hypertension and the effect of modern treatment. Verhandl. Deutsch Ges Kreislaufforsch. 28 160, 1962

2. Bjork, S., Sannerstedt, R., Falkheden, T & Hood, B The effect of active drug treatment in severe hypertensive diseases An analysis of survival rates in 381 cases on combined treatment with various hypotensive agents. Acta Med. Scand. 169· 673, 1961

3 Brown, A E. & Singer R B., Hypertension: Trend of Excess mortality since the 1959 Build and Blood Pressure Study 12 Int. Kongress für Lebensversicherungs-Medizin, (Verlag Versicherungswirtschaft e.V Karlsruhe), München 1976.

4 Build and Blood Pressure Study Society of Actuaries, vol. 1 Chicago 1959

5 Eliasch, H., Varnauskas, E. & Werkö L., Minutvolym och perifert motstånd vid hypertoni — en longitudinell studie. Symposium, Saltsjobaden 1970.

6. Pry J Natural history of hypertension Lancet II. 431 1974

7 Hamilton, M., Thompson, E. N & Wisniewski, T K. M The role of blood pressure control in preventing complications of hypertension, Lancet I 235 1964.

8. Janeway Th. C., A clinical study of hypertensiv cardiovascular disease. Arch. Int. Med. 12: 755 1913

9 Keith, N. M Wagener H P & Barker N W., Some different types of essential hypertension: their course and prognosis. Am. J Med. Sci. 197 332, 1939

10. Veterans Adm. Coop Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. JAMA 202: 116, 1967 213 1143 1970.

	Male		Female	
	Treated	Control	Treated	Control
No. of cases	10	12	20	19
No. of strokes	0	4	3	3
No. of compl.	0	8	5	8
* P<0.025				

Table 3 Treatment vs nontreatment of hypertension comparison of complications in the two sexes (Hamilton et al. 1964).

Diastolic BP	Treatment	N	Dead	Other event A	Other event B
115—129 mm Hg	Placebo	70	4	10	
	Active	73	0	0	
90—114 mm Hg	Placebo	194	19	9	[illegible]
	Active	186	8	9	[illegible]

) nonterminating events

Table 4 Veterans Administration Cooperative Study Group: Mortality and morbidity in treated and untreated patients.

Table 5 Veterans Administration Cooperative Study Group: Classification of Morbid Events.

Diastolic BP	Treatment	Cerebro vascul.	CHD	Cardiac Other	Accel. hypert.	Renal	Other
115—129 mm Hg	Placebo	4	2	6	13	2	0
	Active	1	0	0	0	0	1
90—114 mm Hg	Placebo	20	13	11	4	3	5
	Active	5	11	0	0	0	[illegible]

The results after 6 years of observation encouraged the authors to recommend treatment of males with hypertension under the age of 60 regardless of other symptoms. The recommendations for women could not be made so firmly because of poor control of hypertension in the female group (Table 3)

In order to clarify the discussion on the value of active treatment of nonmalignant hypertension Freis and collaborators started a well controlled double blind study of male veterans in 1963 (10). The study included patients with diastolic blood pressure between 90 and 130 mm Hg with no signs of complications and whose ability to cooperate had been vouched for After exclusion of nearly half the original material, 523 patients were randomized to active or placebo treatment. 143 patients with diastolic blood pressure of 115 or more were followed for 3 years (Table 4) After this time "it became apparent that the risk rate increased sharply and all patients in this group of high diastolic blood pressure were given active treatment. The 380 patients with lower blood pressure were followed for 5½ years and a better out look for the actively treated was also demonstrated for this group of moderate hypertensives.

Subdividing the morbid events between different causes (Table 5) treatment seemed to have given significant protection against cerebrovascular accidents, cardiac insufficiency accelerating hypertension and possibly renal failure in hypertensive patients of both grades. The lack of success in preventing future development of coronary heart disease may be an expression of the different ways in which elevated blood pressure acts as an accelerator of various pathological processes One must bear in mind that in this study the mean age was over 50, and at this age the arteriosclerotic process may have reached a point of no return. Although this study carries many disadvantages in the selection of patients, it still represents the best support for an active attitude to hypotensive treatment.

As pointed out before there are obvious difficulties in drawing prognostic conclusions from clinical series of hypertensive patients. Only extensive follow-up studies of randomly selected people from the general hypertensive population can give a correct picture Insurance applicants are by no means fully representative of the population in general. Comparisons within this selected group may however give some valuable information. At the recently held 12.th International Congress of Life Insurance Medicine Brown & Singer presented a study (3) based on experiences from the New England Life Insurance Company 16 600 deaths were registered in half a million policies during the years 1954 to 1972 (Table 6). This period of 18 years represents a change from the time when the earlier mentioned Build & Blood Pres-

Patient Compliance

Hans Aberg

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Uppsala, Sweden*

Abstract. Only a minority of all hypertensive individuals are well treated. In few other chronic disorders is the patient compliance to therapy such a challenging task. The reason is that a hypertensive patient is usually free from symptoms. Different methods can be used to study compliance. On the one hand we have simple interview methods and on the other we have sophisticated techniques for measuring the urine content of the drug. The best way of evaluating patient compliance over the years, however, is probably to study the number of drop-outs from follow-up or treatment failures with regard to reduction of the blood pressure. In a preventive trial on middle-aged men, over 3½—6 years of therapy we have had a drop-out rate of 8% and a mean blood pressure reduction of 30/18. In another study of drug behaviour in a group of hypertensive individuals an acceptable level of compliance, measured as forgotten doses, was found in about 80% of the subjects. In spite of this rather high figure only a few subjects stated that they had received information on their hypertension at the clinic. However, about half of the subjects did not want any more information. The problem of patient compliance to therapy has therefore many aspects, ranging from the psychological background just touched upon to more practically oriented matters such as dosettes etc. and I will review some of them.

Finally I would like to make some suggestions for improving both the patient's compliance and the doctor's attention to antihypertensive therapy.

A repeated finding in epidemiological studies has been that only a minority of hypertensive individuals are well treated. The figure given for men is about 20% (Table 1) in different parts of the Western world (1, 2, 3, 4, 5). It seems to be higher for women, but on the other hand studies in women (6) have been relatively few. It is a disappointing observation by many physicians that certain patients will not follow prescribed regimens regarding relatively simple medications which would

Table 1. The control of hypertension in different regions.

	Total	HYPERTENSIVES	
		Treated %	Adequately % treated
Uppsala			
♂ 49—50 y (ref. 1)	2322	50	29
♂ 60 y (ref.2)	331	61	38
Gothenburg			
♂ 47—54 y (ref. 3)	7455	39	22
♀ 38—46, 50—54 y (ref. 6)	1230	82	76
US* (ref. 4)	—	26	13
Australia (ref. 5)	—	45	15

* Estimations

11 Volhard, F & Fahr K. T Die Brightsche Nierenkrankheit Klinik Pathologie und Atlas, Julius Springer Berlin 1914

DISCUSSION

Göran Berglund
You mentioned the Fry study We should keep in mind, that this study is a comparison between mortality rates in an economically well-off suburb of London and the total mortality rate in England. It may be so that these data are not representative for the whole hypertensive population.

Gösta Tibblin
What do you think about the better pronosis for high blood pressure among women than among men?

Ingvar Liljefors
We do not have any conclusive explanations for this but women are also not comparable to men as far as other risk factors are concerned. One interesting finding in this connection is that cerebral vascular accidents are a more common cause of death in hypertensive women than in hypertensive men. This is shown in studies from Eliasch and others.

Gösta Tibblin
One explanation can be that the women are easier to treat. Certain experience points in this direction, but of course the disease may be different in women and men in some respect. The strange thing is, that up till now we have no controlled randomised study showing the benefit of treatment for women. That is the study we need to have.

Ingvar Liljefors
I would also like to mention the studies of Hamilton and Bechgaard, which show that women have a better prognosis than men.

Gösta Tibblin
Regarding the wording: Is it necessary to go on talking about "malign and benign" hypertension when even the benign hypertension is so malignant? Malignant hypertension—according to the prevailing nomenclature—is just one or two per cent of the whole hypertensive group. The prognosis is still bad in hypertension as a whole.

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Abstract. Only a minority of all hypertensive individuals are well treated. In few other chronic disorders is the patient compliance to therapy such a challenging task. The reason is that a hypertensive patient is usually free from symptoms. Different methods can be used to study compliance. On the one hand we have simple interview methods and on the other we have sophisticated techniques for measuring the urine content of the drug. The best way of evaluating patient compliance over the years, however is probably to study the number of drop-outs from follow-up or treatment failures with regard to reduction of the blood pressure. In a preventive trial on middle-aged men, over 5½—6 years of therapy we have had a drop-out rate of 8% and a mean blood pressure reduction of 30/18. In another study of drug behaviour in a group of hypertensive individuals an acceptable level of compliance, measured as forgotten doses, was found in about 80% of the subjects. In spite of this rather high figure only a few subjects stated that they had received information on their hypertension at the clinic. However about half of the subjects did not want any more information. The problem of patient compliance to therapy has therefore many aspects, ranging from the psychological background just touched upon to more practically oriented matters such as dosettes etc. and I will review some of them.

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Table 1 The control of hypertension in different regions

	Total	HYPERTENSIVES	
		Treated %	Adequately % treated
Uppsala			
♂ 49—50 y (ref. 1)	7322	50	29
♂ 60 y (ref.2)	531	61	33
Gothenburg			
♂ 47—54 y (ref. 3)	7452	39	22
♀ 38—46, 50—54 y (ref 6)	1230	82	76
US* (ref. 4)	—	26	13
Australia (ref 5)	—	45	15

Estimations

not mean any marked change in their life-style. It is easier to accept non-compliance with recommendations to stop smoking or to lose weight, for example.

It was with the hope of improving this situation among others, that the "First International Congress on Patient Counselling" was held in Amsterdam on the 21st—23rd April 1976 with hypertension in focus.

The problem of patient compliance with therapeutic regimens is of course of considerable significance as regards chronic disorders such as hypertension and diabetes. Of these two hypertension gives the greater test of compliance, as failing therapy is not usually connected with the appearance of symptoms. However the problem of patient compliance is also encountered in short term treatment for an acute illness. Mattar et al. (7) have clearly demonstrated this in otitis media among 674 children attending an acute-diseases clinic.

The purpose of this paper is to review the subject from my own experiences as well as on the basis of the literature

HOW TO MEASURE COMPLIANCE

There are many different ways of evaluating a patient's compliance with a therapeutic regimen. One obvious way is to measure the serum level of the prescribed drug or the urine content of its metabolites. The latter method has been used by Lowenthal et al. (8) for example and in the famous VA study (9) where the compliance was evaluated in each patient during a run-in period. The urine was investigated for fluorescence as riboflavin was incorporated into the placebo tablet, and riboflavin has this ability Only individuals showing such fluorescence were allowed to take part in the further studies.

However all these sophisticated methods can only be used in a limited number of patients and for a relatively short observation time. Such methods are of little help in chronic disorders, except in individual cases where serum levels might be examined to test the momentary reliability of the patient and/or the efficacy of the treatment.

It is important to keep in mind that all the elaborate ways of testing compliance might influence the final outcome of the test. Thus, it is clear that tablet counting will give a better result if the patient is aware of what is going to happen Also an interview might lead to better compliance, as the patient will hesitate to admit to doctor that he is careless about taking his [illegible] Nevertheless, an interview seems to be a fairly adequate method for evaluating patient compliance, particularly if it is conducted by a [illegible] other than the physician who has prescribed treatment (10, 11). This method also has the advantage of being easy to perform and to repeat, which is important in the lifelong treatment of such disorders as hypertension. We have carried out an interview study of patient compliance at a special clinic for hypertension. Defining the accepted level of compliance as "forgetting no more than one or a few doses a month" we found this level to be 81% (12). The interviews were not conducted by the prescribing physician.

One of the best ways of following the compliance to therapy over the years in treatment of a chronic disorder is probably to study the number of drop-outs from follow-up If we exclude those individuals who have a natural reason for not attending follow-up (for example death, moving to another town etc), the rest of the drop-outs must be considered as therapeutic failures due to non-compliance. There is also a certain, unknown number of patients who continue to visit their doctors but nevertheless have poor compliance to the prescribed treatment. In a study of middle-aged men treated for hypertension over a period of 3½—6 years, the number of drop-outs was 10 out of the original 106 subjects (13).

Another way to describe compliance to therapy in hypertension is to investigate how many hypertensive individuals there are who have a satisfactory blood pressure control. In other words, in how many of those on therapy has it been possible to reduce the blood pressure below a predetermined level of acceptance? In the study on middle-aged men mentioned above we have at present 9 subjects whose blood pressure has not reached a satisfactory level out of about 100 on medication In Table 2 the mean blood pressure results are reviewed over the years in the subjects of this study

FACTORS INFLUENCING COMPLIANCE

Pharmacological factors. As seen in Table 3 very few patients follow the prescribed interval between

Table 2. Blood pressures at screening and after treatment in a group of middle-aged men.

BLOOD PRESSURE					
Initial	1 y	2 y	3 y	4 y	5 y
174.5±19.0 / 111.8±7.7	150.1±20.0 / 97.3±8.6	146.3±16.8 / 95.6±9.2	143.9±19.2 / 93.7±9.9	141.8±16.2 / 92.6±9.4	145.0±17.5 / 94.2±8.7
(n=106)				(n=53)	(n=25)

Table 3. Dose intervals of interviewed hypertensives (n=81) at hypertension clinic. The circle denotes the recommended interval.

No. of doses/day	No. of patients. Time interval (in hours) between first and last dose.													
	5	6	7	8	9	10	11	12	13	14	15	16	17	18
2	1	—	1	1	1	6	4	(2)	1	1	—	—	—	—
3	—	—	1	3	2	6	6	3	5	1	1	(1)	—	—
4	—	—	—	—	—	—	3	7	3	7	5	1	—	(—)

Table 4. A review of the number of drugs taken concomitantly with the antihypertensive medication in the same group as in Table 3.

No. of antihypertensive drugs	No. of other drugs 0	1	2	3	4	Total
1	14	3	3	—	—	20
2	28	3	2	—	1	34
3	19	1	2	—	—	22
4	2	2	—	—	—	4
5	1	—	—	—	—	1
	64	9	7	0	1	81

doses (14). Naturally an exact interval between doses is only of importance if this is necessary for the effectiveness of the medication. A strict prescription should not be a purpose in itself. Another factor which should not be neglected is the concomitant use of drugs other than antihypertensive agents in a population with high blood pressure. In Table 4 the use of such drugs is reviewed in the previously mentioned material being interviewed. It is clear that if a patient has many other drugs to take in addition, this will complicate his antihypertensive therapy and thus should be taken into account by the physician.

Further it is of value to combine, if possible, drugs that can be given at the same time interval. There are rational combinations of therapy that will decrease the number of pills and thus should improve the patient compliance. It should be unnecessary in this assembly to stress the importance of longacting drugs in lifelong therapy. Some studies have shown that the compliance is much higher when the patients have only one or at least a few doses each day (15, 16).

A major task for the pharmaceutical industry is of course to further develop the safety of drugs, i.e. freedom from serious side effects. The population in general is paying increased interest in side effects, probably due largely to the mass media.

Practical factors. Some authors have provided evidence that the use of different aids increases patient compliance to therapy. Thus, Haynes et al. (*17*) recently reported on a series that showed increased compliance as a result of visits by high-school graduates who checked their medication and arranged for the patient to be rewarded by being able to buy a sphygmomanometer and stethoscope at discount price. The value of dosettes should not be neglected and, these are in common use in Sweden nowadays. Another important task

not mean any marked change in their life-style. It is easier to accept non-compliance with recommendations to stop smoking or to lose weight for example

It was with the hope of improving this situation, among others, that the "First International Congress on Patient Counselling" was held in Amsterdam on the 21st—23rd April 1976 with hypertension in focus.

The problem of patient compliance with therapeutic regimens is of course of considerable significance as regards chronic disorders such as hypertension and diabetes. Of these two hypertension gives the greater test of compliance as failing therapy is not usually connected with the appearance of symptoms. However the problem of patient compliance is also encountered in short-term treatment for an acute illness. Mattar et al. (7) have clearly demonstrated this in otitis media among 674 children attending an acute-diseases clinic.

The purpose of this paper is to review the subject from my own experiences as well as on the basis of the literature.

HOW TO MEASURE COMPLIANCE

There are many different ways of evaluating a patient's compliance with a therapeutic regimen. One obvious way is to measure the serum level of the prescribed drug or the urine content of its metabolites. The latter method has been used by Lowenthal et al. (8) for example and in the famous VA study (9) where the compliance was evaluated in each patient during a run-in period The urine was investigated for fluorescence as riboflavin was incorporated into the placebo tablet, and riboflavin has this ability Only individuals showing such fluorescence were allowed to take part in the further studies

However all these sophisticated methods can only be used in a limited number of patients and for a relatively short observation time. Such methods are of little help in chronic disorders except in individual cases where serum levels might be examined to test the momentary reliability of the patient and/or the efficacy of the treatment.

It is important to keep in mind that all the elaborate ways of testing compliance might influence the final outcome of the test. Thus, it is clear that tablet counting will give a better result if the patient is aware of what is going to happen. Also an interview might lead to better compliance as the patient will hesitate to admit to the doctor that he is careless about taking his drugs. Nevertheless, an interview seems to be a fairly adequate method for evaluating patient compliance particularly if it is conducted by a person other than the physician who has prescribed the treatment (10 11). This method also has the advantage of being easy to perform and to repeat, which is important in the lifelong treatment of such disorders as hypertension. We have carried out an interview study of patient compliance at a special clinic for hypertension. Defining the accepted level of compliance as "forgetting no more than one or a few doses a month" we found this level to be 81% (12) The interviews were not conducted by the prescribing physician.

One of the best ways of following the compliance to therapy over the years in treatment of a chronic disorder is probably to study the number of drop-outs from follow-up. If we exclude those individuals who have a natural reason for not attending follow-up (for example death, moving to another town etc) the rest of the drop-outs must be considered as therapeutic failures due to non-compliance. There is also a certain unknown number of patients who continue to visit their doctors but nevertheless have poor compliance to the prescribed treatment. In a study of middle aged men treated for hypertension over a period of 3½—6 years, the number of drop-outs was 10 out of the original 106 subjects (13).

Another way to describe compliance to therapy in hypertension is to investigate how many hypertensive individuals there are who have a satisfactory blood pressure control. In other words, in how many of those on therapy has it been possible to reduce the blood pressure below a predetermined level of acceptance? In the study on middle aged men mentioned above we have at present 9 subjects whose blood pressure has not reached a satisfactory level out of about 100 on medication In Table 2 the mean blood pressure results are reviewed over the years in the subjects of this study

FACTORS INFLUENCING COMPLIANCE

Pharmacological factors As seen in Table 3 very few patients follow the prescribed interval between

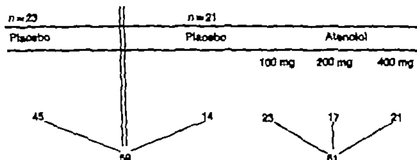


Fig. 1 The number of side effects according to questionnaire in one group (n=23) taking a placebo for 16 weeks and another group (n=21) taking placebo for 4 weeks and Atenolol for 12 weeks at different dosages. (From Hansson et al, Brit. Med. J 2: 367 1975)

than those attained by doctors in hospital as well as by private physicians.

The best result attainable seems to be a figure of about 80% for checking of all hypertensives in a given population after one year. This figure has been reached in a study comprising workers in Gimble's department store in New York City (27). This programme seemed to have all the ingredients to ensure perfect therapy for hypertension.

WHY DO PATIENTS DISCONTINUE ANTIHYPERTENSIVE THERAPY

Several different reasons have been given for discontinuing therapy. These are not identical in countries with different types of hospitals and social systems. Thus, in a study by Caldwell et al. in Detroit, U.S. 42 patients who had had a hypertensive crisis were questioned as to why they had discontinued their treatment (28). It is now several years since this study was performed, but the reasons given are nevertheless of interest. The majority stopped because they felt well (39%). In 33% the patients could not afford medical care. This is of course a figure which should not be reached in a system such as ours. A more remarkable reason however was that 24% were advised by a physician to stop their therapy. Another 14% lacked family support and only 7% discontinued therapy because of side effects. It seems that at least in our country there is a greater general awareness of the side effects of drugs. Therefore, a study such as that of Caldwell et al. is not only dependent on geographic and social circumstances but also on the time at which the study is performed.

In our country an increasing number of patients discontinue their drugs because of problems with alcohol, and people seem to be well aware of the danger of combining alcohol and tablets, at least as long as they are not true alcoholics. It is surprising how often a patient asks if a tablet can be taken together with alcohol. Thus the patients must be well informed about this matter as that question is more often asked than what effect the antihypertensive drug has, or what the reason is for taking it.

CONCLUSIONS

In order to increase patient compliance to antihypertensive therapy some points should be stressed

1. Start medication slowly to anticipate and overcome side effects.
2. Attempt to adjust the therapy to the patient's daily routine and make the dosage schedule feasible.
3. Give information but not necessarily all once. Individualize, and never frighten the patient.
4. Do not restrict the patient's life style with immediate recommendations to cease smoking and give up alcohol. If necessary tackle these problems later on.
5. Involve family members, particularly the wife or husband, in the treatment.
6. Encourage the patient again and again and be his counsel for the defence rather than the judge.
7. Last but not least, the education of doctors on hypertension should be improved.

REFERENCES

1. Hedstrand, H. & Aberg, H. Treatment of hypertension in middle-aged men. Acta Med. Scand. 199 281—288, 1976.
2. Waern, U. & Aberg, H. Hypertension in 60 year old men. Findings in a health survey and some comparisons with 50 year old men in the same community. To be published.
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is to encourage each patient to identify any daily habit or ritual which he can connect with his antihypertensive medication. It would be an error for example to prescribe for a person who only eats twice a day that the drug be taken "three times a day with meals" What will the patient believe— is it important to take the drug three times a day or is it of no value if not taken with meals?

In a recent study it was found that the two factors having the greatest influence on compliance in discharged hospital patients were the complexity of the prescribed dosage schedule and the drug treatment before admission (18) Patients appear to hoard old prescribed medicines (19). It is difficult to know how to prevent this but hospital patients could be requested to hand in all their old medicines at the time of admission.

Some reports have also described programmes in which the patient was made responsible for the administration of his own drugs while under supervision in the hospital (20).

COMPLIANCE VERSUS INFORMATION

In our interview study of compliance we found that only a very small percentage of patients had received information on hypertension (Table 5). Even if this low figure could have been due partly to the fact that most of the patients were "old hypertensives (had been hospitalized or at other outpatient clinics before) and supposedly were considered to be very experienced when starting at the Hypertension Clinic, it seems very unsatisfactory However an interesting finding at the interview was that almost half of the patients did not want to have more information. Other studies have established the limited value of information at least in some patients. Thus Sacket et al. (21)

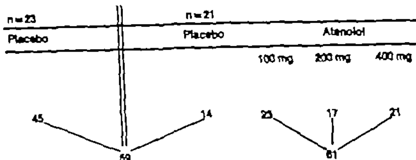
Table 5 Information received and wanted in an interviewed group of hypertensives.

Action of drug	6%
Side effects	8%
Diet	4%
No information	82%
Want more information	57%
Want no more information	43%

found that even "mastery learning" by means an educational programme did not increase pliance. Failure of education to affect prevent. therapy has also been shown recently by A. et al. (22). Are then non-compliance and patient apathy inevitable and all health education aimi at eliminating them of no value? Otherwise how can this lack of interest in information on such an important risk factor for future cardiovascul disease and death be interpreted? This constitutes patient psychology of a hitherto poorly studied type. It has been thought that there may be an unconscious desire to forget something (antihy pertensive drugs) that will recall a future risk of suffering from some cardiovascular accident (23) This is strengthened by the fact that most individuals do not have symptoms from their hyper tension (24). This lack of symptoms in hypertension makes it even more essential that the antihypertensive drug should not have side effects. It is common for patients under therapy to attribute all new unpleasant experiences to the drug even though side effects" are also often experienced from placebo (Figure 1).

In order to handle this problem the previously mentioned negative attitude to information as well as the small impact of such information on a patient's compliance must be studied further (21). The most likely explanation for this lack of effect is that the information is poorly conveyed or given at wrong times. It is probably necessary to individualize such information and it should perhaps be given in small portions over a long period of time so as not to cause undue anxiety Passive indoctrination of the patient should be avoided and an attempt should be made to get him to participate in his own treatment. Mc Kenney et al (25) found that general information about high blood pressure was not an important element in promoting compliance. In their study a pharmacist was instructed to carry out tasks such as clarifying instructions monitoring compliance and adjusting the medical regimen etc. and this was found to have an excellent effect. Their results thus demonstrate that other personnel than the doctor can be used as a source of information though the authors considered that the doctor should in fact carry out these tasks. Thus, Wilber (26) reported remarkably good follow-up results in a clinic run by nurses. These were better in fact,

Fig 1 The number of side effects according to a questionnaire in one group (n=23) taking placebo for 16 weeks and another group (n=21) taking a placebo for 4 weeks and Atenolol for 12 weeks at different dosages. (From Hansson et al. Brit. Med. J 2: 367 1975.)



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REFERENCES

1 Hedstrand, H. & Aberg, H.. Treatment of hyper tension in middle-aged men. Acta Med. Scand. 199: 281–288 1976.
2 Waern, U & Aberg, H.. Hypertension in 60 year old men. Findings in health survey and some comparisons ith 50 year old men in the same community T be published.
3 Berglund, G.. Hypertoni och hypertensiva organmanifestationer hos 50-åriga män. En epidemiologisk och fysiologisk studie. Thesis. Elanders, Kungsbacka 1974. (With English Summary).

4 Irvin, I Outline of screening evaluation, therapy and patient education guidelines. High Blood Pressure Information Center National Institutes of Health, Bethesda, Maryland 200 14 USA.
5 Reader R. Hypertension and the community Acta Med. Scand Suppl. 576 83 1975
6 Tibblin G & Bengtsson C. Detection and treatment of hypertension in a community Millbank Memorial Fund Quarterly XLVII No 3 160 1969
7 Mattar M E. Markello J & Yaffe S J Inadequacies in the pharmacologic management of ambulatory children J Pediat. 87 137 1975
8 Lowenthal D T., Briggs W A Mutterperl, R. Adelman, B & Creditor M. A Patient compliance for antihypertensive medication the usefulness of urine assays. Curr Ther Res. 19· 405 1976.
9 Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mmHg. JAMA 202. 1028 1967
10 Park, L. C. & Lipman, R S. A comparison of patient dosage deviation reports with pill counts. Psychopharmacologia 6 299 1964
11 Rickels, K. & Briscoe E. Assessment of dosage deviation in outpatient drug research. J Clin. Pharmacol. 10· 153 1970
12. Eklund L. H. Wenling A. & Aberg, H. Hur sköter hypertoniker sin medicinering. Läkartidningen In press.
13 Åberg, H. & Hedstrand, H.. To be published.
14 Eklund, L. H Wenling, A & Aberg H. Hypertonikers önskemål om läkemedelsinformation Nord. Med. 91 113 1976.
15 Clinite J C & Kabat H F Prescribed drugs. Errors during self-administration. J Amer Pharm. Ass. 9 450 1969
16. Beck Nielsen, H & Bjerre P Hvordan administrerer udskrevne patienter fast ordinerede lægemidler? Ugeskr Læg. 135 2171 1973
17 Haynes R. B Sackett D L. Gibson E. S. Taylor D W., Hackett, B C. Roberts, R. S. & Johnson, S. L. Improvement of medication compliance in uncontrolled hypertension. Lancet I. 1265 1976
18 Parkin, D M. Henney C R Quirk, J & Crooks J Deviation from prescribed drug treatment after discharge from hospital Br Med. J 2. 686, 1976
19 Law R & Chalmers, C. Medicines and elderly people a general practice survey Br Med. J 1 565 1976.
20 Buchanan E. C. Brooks, M. R. & Greenwood, R. B A selfmedication program for cardiology inpatients. Amer J Hosp. Pharm. 29· 928 1972.
21 Sackett, D L. Haynes, B R. Gibson E. S. Hackett, B C. Taylor D W Roberts, R S. & Johnson, A. L. Randomised clinical trial of strategies for improving medication compliance in primary hypertension. Lancet I 1205 1975
22. Aronow W S. Allen, W H., De Cristofaro, & Ungermann, S. Follow-up of mass screen for coronary risk factors in 1817 adults. Circulation 51 1038 1975
23 Blackwell B Speach at First International Congress on Patient Counselling, Amsterdam, 21st 23rd April 1976.
24 Weiss N S. Relation of high blood pressure headache epistaxis, and selected other symptoms The United States Health Examination Survey of Adults. New Engl. J Med. 287 631 1972.
25 Mc Kenney J M. Slining, J M. Henderson, R. Devins D & Barr M.. The effect of clinical pharmacy services on patients in essential hypertension Circulation 48 1104 1973
26. Wilber J., Personal communication.
27 Alderman M. H. & Schoenbaum, E. E.. Detection and treatment of hypertension at the work site. New Engl. J Med. 298. 65 1975
28 Caldwell, J R. Cobb S., Dowling, M. D & De Jongh, D The dropout problem in antihypertensive treatment. A pilot study of social and emotional factors influencing a patient's ability to follow antihypertensive treatment, J Chron Dis. 22. 579 1970.

DISCUSSION

Bengt Scherstén
Are there any differences in compliance in relation to whether the patient is detected by screening or not or in relation to the presence or absence of symptoms?

Hans Åberg
I cannot give you any figures from our own studies, but I think these factors have been studied by Caldwell. His cases were detected in connection with hypertensive crises, and had all the symptoms you could wish for but the results after a short time were still poor

Martin Ericsson
Our impression is that those patients who have a family background of hypertension are a risk group on which controls are worth performing.

Hans Åberg
There is no doubt that in those individuals who have a family history of hypertension or cardiovascular disease hypertension will tend to appear earlier at least will be discovered earlier I think that they are also probably more adequately treated

Konrad Saameli
It is often said that using twice a day dosage (one dose in the morning another in the evening) is superior with regard to compliance than using three doses daily Can you confirm this impression and could you perhaps also comment on the

question of whether or not a once a day treatment schedule is superior to two daily doses?

Hans Åberg
Twice a day dosage is better than three times a day. Opinion is almost unanimous on this. This perhaps relates to the fact that patients do not need to take their medication to their job, which is difficult. On the other hand, I do not feel that there is such a big difference between twice a day and once a day dosage as there is between three times and twice a day although once a day dosage may well be better

Anders Vedin
Information on patient compliance can be collected from other areas. The severity of disease is the key factor in predicting patient compliance. In post myocardial infarction studies, 90 per cent of patients have complied with the prescribed dosage regimen.

In regard to the number of doses a day and its influence on compliance, this has been studied in several studies involving antibiotics. The results here indicate that the difference in compliance between single dose and twice a day dosage is small.

Hans Åberg
It is not right to compare rheumatic fever or myocardial infarction with hypertension. Hypertension is a chronic disorder without symptoms for most people and I think we need other studies than those you are referring to

Gosta Tibblin
Maybe we can go on and talk a bit about information. You had a group which said that they do not want to have information. What is information in their mind. Perhaps they were just thinking about booklets? What we must do in those cases, is to change the behaviour of person, an asymptomatic person who has no feeling of being sick. This is not so easy and I think w must discuss these problems and the methods needed to solve them. Perhaps study-groups and group ther py could be used for the treatment and information of these patients

Hans Åberg
It is very important of course to give information and as you say I think w have to give it in other ways. T hand over a pamphlet on hypertension is perhaps more relief for the doctor than it is for the patient. We have to individualize the information, to give it over a long time not all immediately and without causing them further anxiety

Per Lund-Johansen
In regard to the question on what is a healthy and what is an unhealthy person, I think that some of us may have read or seen the play Dr Knock, by Romain, and perhaps remember his definition of a healthy person. "A healthy person is a person who does not know that he is sick. Bearing in mind Romain and Dr Knock, our definition today might be that a healthy person is a person who does not know his risk factors. But as long as we believe in preventive cardiology and as long as we believe that we can do something to postpone the complications and to prolong life in a reasonable way I think we of course have to do it.

Bengt Scherstén
Could it be that the principles on which our patient care is based are in any way wrong? Perhaps we should not organize these antihypertensive clinics? Perhaps we should let the "Primary Care" take care of hypertensive patients? The continuity of the care is perhaps very important in getting patients to take the tablets.

Robert Griffith
I imagine there might be some correlation between the number f tablets the patient is expected to take and the likelihood that he will not comply with taking them. Although we have all been told how bad combination medicines are, I think that, in the field of hypertension therapy this is one area where there might be a place for fixed combinations, if only because patient compliance is so terrible

Hans Åberg
Well, I think it is important to discuss treatment with fixed combinations for hypertension. I think there might be a place for this, but obviously it is difficult to make a fixed combination which is adequate for many people.

Bernt Hökfelt
To be provocative, fixed combinations to my mind, require standard patients and most people are not standard.

Haemodynamics in Essential Hypertension

Chairman Hans Dunér

Department of Internal Medicine, Sabbatsberg Hospital, Stockholm, Sweden

Our knowledge of "haemodynamics in essential hypertension" has increased rapidly in recent years. 15—20 years ago essential hypertension, from the haemodynamic point of view, was understood as a more or less fixed condition of increased peripheral vascular resistance and a normal or decreased cardiac output. Since then, we have obtained a more detailed and graduated picture of the role of the heart's activity and the condition of the peripheral vascular bed during the development of hypertension. The introduction of beta receptor blocking drugs in the treatment of hypertension, has not only been of great importance from a therapeutic point of view, but has also considerably increased our knowledge of haemodynamics.

In many clinics, beta-blockers are now the first line treatment for hypertension. It is interesting to see how quickly this development has occurred. When the first beta-blocker was launched at the beginning of the sixties, it was in the indication cardiac arrythmia, and any blood pressure lowering effect was unknown. The first publication on the blood pressure lowering effect of beta-blockers came in 1964. We have here today one of the pioneers, Gustaf Schröder, who together with Lars Werkö and at the same time as Prichard and Gillam reported this effect. At first there was a certain skepticism of the clinical value of beta-blockers for the treatment of hypertension. I will not go into details on the reasons for this. We can only see how accumulating evidence of the usefulness of beta-blockers as hypertensive agents has altered general opinion in this field. The first part of this session consists of two papers dealing with central and peripheral haemodynamics in essential hypertension, and I think it will be best to discuss these two papers together. The next part will deal with the effect of beta-blockers on

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haemodynamics in essential hypertension It seems appropriate to discuss these two papers together as well, followed by four contributions submitted in advance to the discussion.

Per Lund Johansen from Bergen is the first speaker As we all know he has carried out some very important studies on alterations in the pattern of haemodynamics with increasing age and on central haemodynamics in essential hypertension.

Central Haemodynamics in Essential Hypertension

Per Lund-Johansen

From the Medical Department A, University of Bergen, School of Medicine, Bergen, Norway

INTRODUCTION

The arterial blood pressure is mainly determined by the cardiac output and the total peripheral resistance, and although it is a rather crude simplification, it is generally stated that MAP = COxTPR (MAP = mean arterial pressure, CO = cardiac output, TPR = total peripheral resistance). The cardiac output is of course the product of the stroke volume (SV) and the heart rate (HR).

Until 1960 most studies on the haemodynamics in essential hypertension were done by heart catheterization and included usually small groups of subjects, mainly with established hypertension of long duration. The common finding was that the elevated systematic blood pressure was caused by an increased total peripheral resistance, while the cardiac output was normal so long as heart failure was not present.

CROSS-SECTIONAL STUDIES

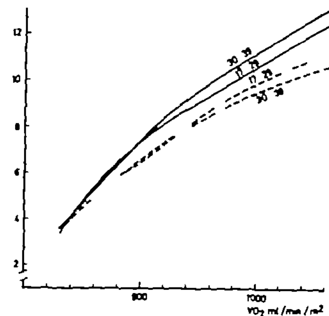
Early phase. About 15 years ago it was suggested that an increased cardiac output might be an important pathogenetic factor in early essential hypertension, and several studies from different parts of the world have appeared (reviews in references 15 and 19).

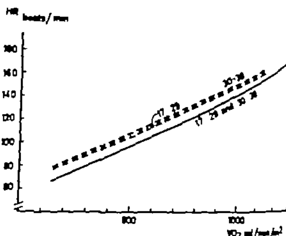
At rest, in the supine position, most investigators have found that in subjects below the age of 40 with a mean arterial pressure around 100 to 110 mm Hg at the time of the study, the cardiac index is significantly higher than in controls, and the calculated total peripheral resistance not significantly different from controls (15). Studies at rest performed in the sitting position in young subjects with mild hypertension have also revealed high cardiac index (12, 18), but in subjects with borderline hypertension, who had high cardiac index in the supine position, the cardiac index became normal when sitting (10).

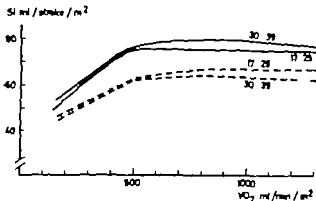
Most investigators have found that the high cardiac output is due to an increase in the heart rate. It should be noted, however, that the cardiac output is not increased when it is related to the oxygen consumption of the body. This has been demonstrated in at least three studies (10, 12, 18). Thus there is no luxury perfusion in essential hypertension in contrast to the so-called hyperkinetic heart syndrome.

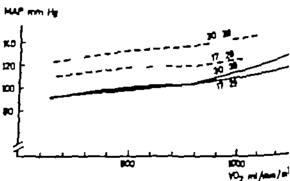
The mechanisms behind the high cardiac output, the high heart rate and the increased oxygen consumption in subjects with mild or labile essential hypertension are unknown. An increased activity in the sympathetic nervous system has been discussed, but definite proof is still lacking.

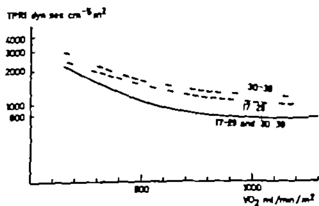
In spite of the fact that the calculated total peripheral resistance falls within "normal" ranges in early essential hypertension, it could be argued that the total peripheral resistance is not normal, because if it were, it should have adapted to the high cardiac output with dilatation and thus be keeping the blood pressure normal. This is made clear when subjects are studied during muscular exercise. To avoid excessive rise in blood pressure, the resistance vessels must then dilate at least in some parts of the body. In a personal study on 137 untreated hypertensive males, age 17 to 59 years old, of whom 64 were below 40 years, it was found that during steady state exercise at 300, 600 and 900 kpm/min the cardiac index was no longer increased in any age group including the youngest (Figure 1 and 2). The reduced cardiac output during exercise was due to a reduced stroke volume. During exercise the total peripheral resistance was clearly increased in all age groups including the youngest. The rise in blood pressure was similar to the rise in controls when related











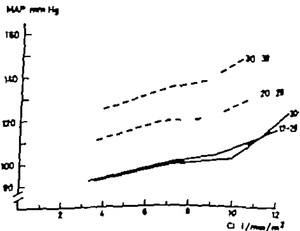


Fig 1 Haemodynamic changes at rest and during exercise in subjects with essential hypertension in WHO stage I aged 17—29 years and 30—39 years compared to normotensive controls. CI=Cardiac Index HR=Heart Rate SI=Stroke Index MAP=Mean Arterial Pressure TPRI=Total Peripheral Resistance Index, VO_2=Oxygen Consumption. Mean values from 22 normals and 64 hypertensives. (Reproduced from Onesti, G Kim, K. E. & Moyer J H. [eds] Hypertension, Mechanisms and Management Grune & Stratton Inc. 1973 with kind permission).

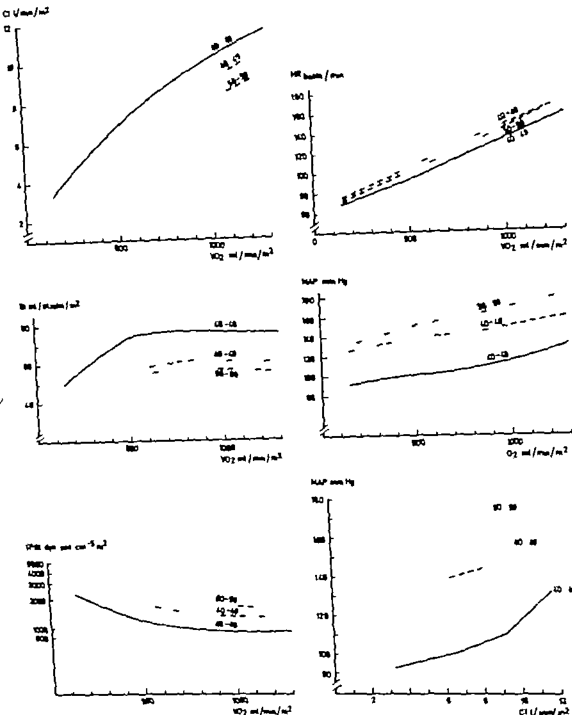


Fig. 2. Haemodynamic changes at rest and during exercise in subjects with essential hypertension aged 40—49 years (WHO stage I) and aged 50—59 years (WHO stage I or II) compared to normotensive controls aged 40—49 years. CI=Cardiac Index, HR=Heart Rate, SI=Stroke Index, MAP=Mean Arterial Pressure, TPRI=Total Peripheral Resistance Index, VO_2=Oxygen Consumption. (References as in figure 1).

the blood flow the rise was steeper than in controls the steepest rise was seen in the oldest group. This was reflected in the calculated total peripheral resistance.

Most of these findings have been confirmed in exercise studies on the bicycle ergometer by other groups (1 18). Thus even if the calculated total peripheral resistance was not different from controls *at rest* it is evident from *exercise* studies that it is nevertheless already abnormal in subjects supposed to have "early" essential hypertension. Furthermore the exercise studies reveal that the heart pump function is subnormal due to a subnormal stroke volume and this is seen in subjects with mild essential hypertension already in their twenties.

Later phase In subjects with established essential hypertension of long duration, but without clinical heart failure the results from recent years are in agreement with earlier findings. At rest, the high arterial pressure is maintained by an increased total peripheral resistance in presence of a normal low cardiac index (1 12, 18). With increasing clinical severity of the disease the cardiac index and the stroke index tend to be very low and the total peripheral resistance very high. Essentially the same is found during muscular exercise. Exercise studies also demonstrate that in established essential hypertension the circulatory system might be hypokinetic even if no clinical signs of heart failure are present, and the arteriovenous oxygen difference is increased

LONGITUDINAL STUDIES

Early phase Although the results from the cross-sectional studies make it very likely that the circulatory system in subjects with untreated essential hypertension should change from a high-flow normal resistance pattern towards a low-flow high-resistance pattern only longitudinal studies can tell if this will really happen. Until now systematic long-term studies have been lacking. In the following a preliminary report of a 10 year follow-up study in males with untreated essential hypertension will be given

MATERIALS AND METHODS

The 1967 study included 77 hypertensives (17-66 years) and 33 normotensives (18-49 years) studied

cular exercise (12) Most of the 36 hypertensives below 40 years of age had mild hypertension in WHO stage I and did not start drug treatment, but were controlled clinically every year or every second year In age group I (17 29 years, n=19) the mean value of the blood pressure recorded intraarterially was 150/92 mm Hg in 1967 Over the following 10 years 2 were lost abroad, 17 were alive healthy still in WHO stage I 16 had been untreated and all but one (living far from Bergen) have been restudied haemodynamically

In age group II (30—39 years old n=17 all in WHO stage I) the mean value of the intraarterial pressure was 160/99 mm Hg when first studied One subject died from lung and heart insufficiency The remaining 16 patients are alive, all still in WHO group I. 13 have been untreated and they have all been restudied haemodynamically

In the two oldest age groups the majority of the patients started drug treatment, and spontaneously occurring changes in haemodynamics could thus not be studied in these two groups. They will not be discussed further in this report.

Exactly the same methods were used in both studies. The subjects were studied at rest sitting and during steady state muscular exercise at 300, 600 and 900 kpm/min. Oxygen consumption was measured by Douglas bag and Scholander technique heart rate by ECG cardiac output by dye dilution method (Cardiogreen double determination in each situation) arterial blood pressure continously by catheter in the brachial artery The details have been published in 1967 (12).

RESULTS

A survey of the most important findings are shown in Figures 3—5 and Tables 1—3

The *oxygen consumption* (VO_2) at rest had decreased from *171 to 157 ml/m²* ($p<0.05$) in age group I but was almost unchanged in group II. During exercise there were only small changes.

The *blood pressure* showed remarkedly small changes. During rest and low exercise levels there were no significant changes in systolic (SAP) diastolic (DAP) or mean (MAP) arterial pressures. Only during 900 kpm/min exercise there was a significant increase in MAP from 133 to 141 mm Hg in age group I and from 141 to 147 mm Hg in group II (Table 1).

Table 1 10 year follow-up study Mean arterial pressure (mm Hg).
1=First study 2=Restudy (Age at study 1)

		Rest		Work		(kpm/min)			
		Sitting		300		600		900	
		1	2	1	2	1	2	1	2
Age	Mean	112.3	114.7	120.5	123.6	122.9	126.0	133.1	141.0
17—	Sd	7.5	9.5	10.0	10.7	8.4	8.2	9.5	12.1
29 yrs	2—1	+2.4		+3.1		+3.1		+7.9	
n=13	p	Ns		N		Ns		<0.05	
Age	Mean	116.5	117.7	127.6	132.9	130.6	134.5	140.7	147.3
30—	Sd	9.5	10.7	12.3	10.0	12.2	8.6	15.5	12.4
39 yrs	2—1	+1.2		+5.3		+3.9		+6.6	
n=13	p	Ns		N		N		<0.05	

Table 2. 10 year follow-up study Cardiac index (l/min/m²).
1=First study 2=Restudy (Age at study 1)

		Rest		Work		(kpm/min)			
		Sitting		300		600		900	
		1	2	1	2	1	2	1	2
Age	Mean	3.81	3.22	7.06	6.58	9.04	7.89	11.10	9.44
17—	Sd	0.53	0.83	1.05	1.20	0.85	0.68	1.03	0.88
29 yrs	2—1	—0.59		—0.48		—1.15		—1.66	
n=15	p	<0.01		N		<0.001		<0.001	
Age	Mean	3.64	2.81	6.82	5.82	8.49	7.48	10.41	8.96
30—	Sd	0.63	0.44	0.70	0.77	0.97	0.91	1.32	0.92
39 yrs	2—1	—0.83		—1.0		—1.01		—1.45	
n=13	p	<0.001		<0.001		<0.01		<0.01	

The *cardiac index* (CI) had decreased significantly in both age groups at rest as well as during moderate and severe exercise (Table 2). In the youngest group the reduction in cardiac index was only 0.48 l/min/m² (N.S.) at the lowest work level. In the oldest age group the CI was significantly reduced also at this low exercise level. In both age groups the reduction in cardiac index was associated with a significant decrease in *stroke index (SI) at rest as well as during exercise.*

The *heart rate* (HR) at rest and during exercise showed only small and insignificant changes in group I, but in group II there was a significant decrease in the resting value (from 80.4 to 71.3 beats/min).

The *total peripheral resistance index* (TPRI) had increased significantly both at rest and during exercise in both age groups (Table 3).

DISCUSSION AND CONCLUSION

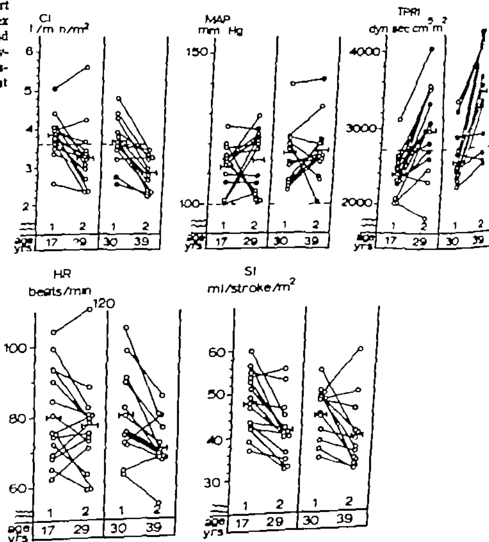
The most important findings in the cross-sectional study from 1967 (12) have been confirmed by others (1, 10, 11, 17, 18, reviews in 13, 15, 19). In another previous study (14) it was found that in untreated subjects with mild hypertension no significant changes in the central haemodynamics could be detected over a period of *one year.*

In the *10 year follow-up study*, however, it has been possible to demonstrate that significant changes in the central haemodynamics had indeed

Table 3 10 year follow-up study Total peripheral resistance index (dyn sec cm^{-5} m^{2}).
1=First study 2=Restudy (Age at study 1)

		Rest		Work	(kpm/min)				
		Sitting		300		600		900	
		1	2	1	2	1	2	1	2
Age	Mean	2392	2971	1386	1531	1095	1285	965	1205
17—	Sd	284	574	168	206	111	125	93	155
29 yrs	2—1	+579		+145		+190		+240	
n=15	p	<0 001		<0.01		<0.001		<0.001	
Age	Mean	2532	3437	1533	1835	1242	1457	1091	1333
30—	Sd	480	684	142	270	152	190	143	220
39 yrs	2—1	+905		+326		+215		+241	
n=13	p	<0.001		<0 01		<0.01		<0.01	

Fig 3 Cardiac index (CI) mean arterial pressure (MAP) total peripheral resistance index (TPRI), heart rate *(HR) and stroke index* (SI) at first (1) and second (2) study *A 10 year follow-up study* in untreated essential hypertension. Rest sitting.



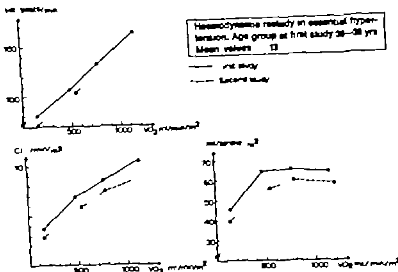


Fig 4 Cardiac index (CI), heart rate (HR) and stroke index (SI) at rest, sitting and during exercise at study 1 and 2. Mean values. Age group 30—39 years at study 1

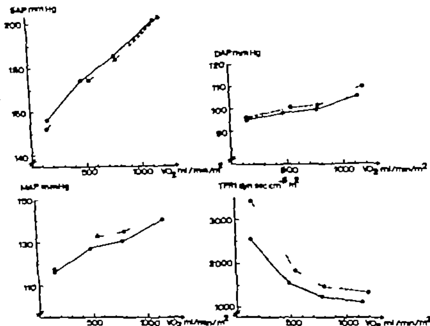


Fig. 5 Systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) and total peripheral resistance index (TPRI) at rest and during exercise at study 1 and 2. Mean values. Age group 30—39 years at study 1

occurred In the youngest group the increased VO_2 had fallen close to the value in age group II 10 years ago The increased heart rate persisted, but in age group II (now being 40—50 years old) the resting heart rate had decreased. In both age groups the reductions in SI and increases in TPRI were impressive and very consistent. Thus in spite of the fact that the subjects seemed to have tolerated their hypertension well—without any overt clinical complications—the haemodynamic study showed that their cardiovascular system had deteriorated more than expected from aging alone. Several cross-sectional studies in healthy normotensive subjects have demonstrated that aging from the twenties to the forties involves no or only negligible changes in the cardiac performance (2, 4 8 9). This is in clear contrast to what happens in the hypertensives. No systematic studies

Table 3 10 year follow-up study Total peripheral resistance index (dyn sec cm^{-5} m^{2}).
1=First study 2=Restudy (Age at study 1)

		Rest Sitting 1	Rest Sitting 2	Work (kpm/min) 300 1	300 2	600 1	600 2	900 1	900 2
Age	Mean	2392	2971	1386	1531	1095	1285	965	1205
17—	Sd	284	574	168	206	111	125	93	155
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n=15	p	<0 001		<0.01		<0 001		<0.001	
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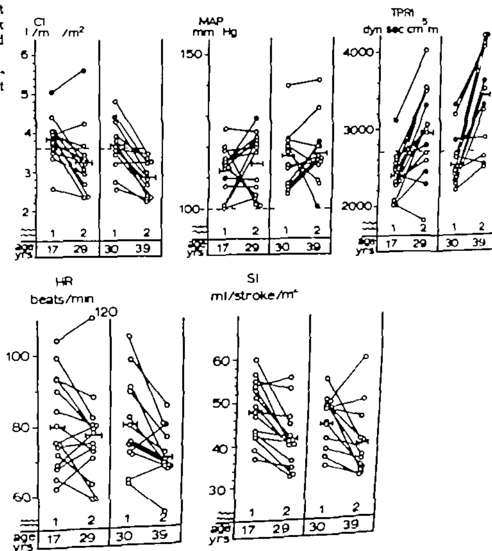


Fig 3 Cardiac index (CI) mean arterial pressure (MAP) total peripheral resistance index (TPRI) heart rate (HR) and stroke index (SI) at first (1) and second (2) study A 10 year follow up study in untreated essential hypertension Rest sitting

Peripheral Haemodynamics in Essential Hypertension

Ramon Sivertsson

From the Department of Clinical Physiology Östra Sjukhuset (East Hospital) Göteborg Sweden

Abstract. Previous studies have indicated the existence of haemodynamically important structural vascular changes in patients and animals with hypertension.

Possible pathophysiological implications of these changes are discussed.

Two studies dealing with the question of reversibility of the structural changes on long-term blood pressure lowering therapy are described. The results indicate that the changes are partially but not completely reversible.

STRUCTURAL VASCULAR CHANGES IN HUMAN HYPERTENSION

In patients with established hypertension blood pressure is elevated because vascular resistance is increased. Cardiac output is normal. Haemodynamic studies on patients with untreated essential hypertension indicate that resistance is increased not because of high tone in the smooth muscle cells of the resistance vessels but rather because of structural changes in these vessels (1 2, 3 4) Thus vascular resistance in the hand at maximal vasodilatation was increased to a considerable degree in the patients compared to the controls (4) in fact more than the mean blood pressure (69 per cent and 46 per cent respectively) Since resistance in this study was measured under almost complet relaxation of the vascular smooth muscle cells the difference in resistance can only be explained by structural difference between the two vascular beds Because of this finding and other haemodynamic findings in combination with the observations done by the pathologists (5 6) it was concluded that in established essential hypertension resistance is mainly increased because of a structural change in the resistance vessels This change implies an increased wall thickness in relation to lumen and the thickened wall encroaches upon the lumen also at maximal dilatation. The wall *thickening*, which seems to involve the resistance vessels of most vascular beds more or less, is partially due to smooth muscle hypertrophy partially to increased amounts of other wall components, e g. collagen. Corresponding changes are also seen in the bigger arteries.

HOW DO THE VASCULAR CHANGES ARISE?

Animal experiments show that structural changes can be secondary to the blood pressure elevation (7). Although it cannot be excluded that the vascular changes are primary in some patients (genetically based tendency to smooth muscle hyper trophy), they are most likely secondary in the majority of patients with essential hypertension. A primary "triggering factor (g. a neurogenic, a renal or a hormonal one) is thus needed.

PATHOGENETIC IMPLICATIONS OF VASCULAR CHANGES

If the changes are secondary to blood pressure elevation what is then the role of these changes in hypertension?

1 When established the vascular changes potentiate the primary blood pressure elevation.
2. They transform a labile hypertension to a stable one. Before the vascular changes are established blood pressure, e g. in *neurogenic* hypertension is supposed to be normal in the periods between the neurogenic pressure peaks, but after the vessels are changed this "resting" pressure is also elevated.
3 If the changes are irreversible or only partially reversible they will constitute a permanent blood pressure elevating factor which remains even when the primary cause is eliminated.

similar to this have been presented. However one study in treated subjects taken off therapy for a short period of time (3) and another study of shorter duration (5) did show similar trends as those in the present study It is therefore reasonable to conclude that the 10 year duration of hypertension was responsible for the far greater alterations in the central haemodynamics than would be expected from aging alone.

What is the mechanism behind the decrease in the SI and in the increase in the TPRI? What is the meaning of these changes with respect to the progress of the hypertensive process? This has to be answered by future studies. However these functional alterations show a remarkable similarity to what is seen in the spontaneously hypertensive rats (SHR) when the time factor is expressed as a fraction of life duration (6 7 16 20). In the SHR a reduced SI is a very early abnormality and so is the increase in the TPRI. Furthermore in the normotensive rat the pump function seems to be little altered by time. In the rats it is of course possible to study the morphological and biochemical abnormalities behind the functional changes in the central haemodynamics. It is beyond the scope of this article to discuss these findings in detail, but largely all these findings taken together seem to fit well with Folkow s theory about the restructuring of the high pressure compartments (7) Thus the "vicious circle" seems to be operating also in man but slowly and therefore hard to study Another crucial question is of course whether these changes are reversible and at what stage antihypertensive therapy should then be started.

REFERENCES

1 Amery A Julius, S Whitlock, L. S & Conway J Influence of hypertension on the haemodynamic response to exercise Circulation 36. 231 1967
2. Becklake M. R. Frank, H, Dagenais, G R Ostiguy G L. Guzman C. A. Influence of age and sex on exercise cardiac output. J Appl. Physiol. 20: 938 1965
3 Birkenhager W H. Schalekamp M. A. D H. Krauss, X H Kolsters G Zaal, G A. Consecutive haemodynamic patterns in essential hypertension Lancet I. 560, 1972.
4 Donald K W Bishop J M Cummings G Wade O L. Effect of exercise on cardiac output and circulatory dynamics of normal subjects. Clin. Sci. 14 37 1955
5 Eich R. H. Cuddy R. P Smulyan, H. Lyons, R. H.. Haemodynamics in labile hypertension. A follow-up study Circulation 34 299 1966.
6. Farmer B B Harris, R. A., Jolly W W., Vail, W J.. Studies on the cardiomegaly of the spontaneously hypertensive rat. Circ. Res. 35 102, 1974
7 Folkow B Vascular changes in hypertension—review and recent animal studies. In Pathophysiology and Management of Arterial Hypertension edited by Berglund, G., Hansson, L., Werkö L. Göteborg, Lindgreen & Söner AB 1975 p. 95.
8 Hansson, J S. Tabakin, B S. Levy A. M. Comparative exercise-cardiorespiratory performance of normal men in the third, fourth and fifth decades of life Circulation 37 345 1968
9 Julius, S Amery A. Whitlock, L. S., Conway J.. Influence of age on the haemodynamic response to exercise. Circulation 36. 222, 1967
10. Julius, S Conway J.. Haemodynamic studies in patients with borderline blood pressure elevation. Circulation 38 282, 1968
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13 Lund-Johansen, P.. Physiological symptoms and signs of ICIN in arterial hypertension changes in the physiological data announcing failure. In European Society of Cardiology Symposium on incipient cardiac insufficiency Sandoz Ltd, Basle 1970, p. 119
14 Lund-Johansen P Haemodynamic changes in long-term diuretic therapy of essential hypertension. Acta med Scand. 187 509 1970.
15 Lund-Johansen P Haemodynamic alterations in essential hypertension. In Hypertension. Mechanisms and Management, edited by Onesti, G Kim K. E. Moyer J H. New York and London, Grune & Stratton Inc., 1973 p. 43
16. Pfeffer M A Frohlich, E. D Haemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. Circ. Res. 32, 33 (suppl. I): I 1973
17 Safar M E. Weiss, Y A. Levenson J A London G M. Milliez, P L. Haemodynamic study of 85 patients with borderline hypertension Am. J Cardiol. 31 315 1973
18 Sannerstedt R. Haemodynamic responses to exercise in patients with arterial hypertension Acta med. Scand 180 (suppl. 458), 1966.
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13 Lund-Johansen P Physiological symptoms and signs of ICIN in arterial hypertension changes in the physiological data announcing failure. In European Society of Cardiology Symposium on incipient cardiac insufficiency Sandoz Ltd, Basle 1970 p. 119
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15 Lund-Johansen P Haemodynamic alterations in essential hypertension. In Hypertension. Mechanisms and Management, edited by Onesti, G Kim K. E. Moyer J H. New York and London, Grune & Stratton Inc. 1973 p. 43
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20. Tarazi R. C.. The heart in hypertension its load and its role. Hospital Practice 10- 31 1975

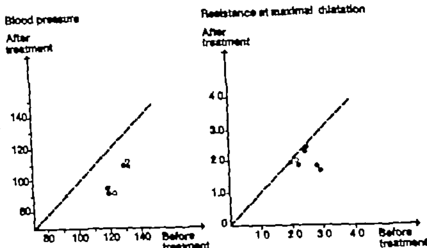
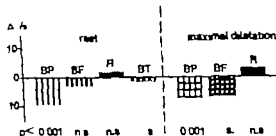
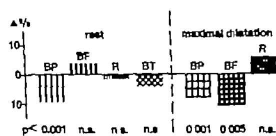
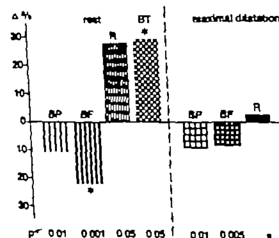


Fig. 2. Mean arterial ambulatory blood pressure and calf blood flow resistance at maximal vasodilatation before and after 6 months of antihypertensive treatment (propranolol or alprenolol and hydrallazine) in 12 patients with essential hypertension.







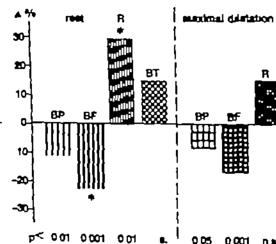


Fig. 3. Change in mean arterial ambulatory blood pressure (BP), calf blood flow (BF) and blood flow resistance (R) at rest and under vasodilatation after 6 months treatment with mefruside in twenty-three hypertensive patients (upper panel) and with atenolol in eighteen patients (lower panel). Vascular tone (BT), i.e. resistance at rest divided by resistance under vasodilatation, is also given. The asterisk (*) indicates significant difference between the mefruside and atenolol groups.

4 Corresponding changes in the big arteries are probably responsible at least partially for the baroreceptor resetting in hypertension, the thickened arterial wall being less distensible than the normal one. Thus a higher pressure is needed to activate the stretch receptors involved in the barostatic reflex.
5 Recently a long term barostatic function has been ascribed to the kidney (8) The kidney barostat is probably also reset by structural vascular changes, localized to the renal vessels.

REVERSIBILITY OF VASCULAR CHANGES ON LONG TERM BLOOD PRESSURE LOWERING THERAPY

From what is said above it is evident that the question of reversibility of vascular changes has a fundamental bearing to the pathophysiological role of the changes. Studies on animals (spontaneous and renal hypertensive rats) indicate that hypertensive vascular changes can be prevented if blood pressure lowering therapy is started in the newborn animal (9) They can be completely reversed if pressure normalisation is initiated early (7), but if treatment is not begun until the animal is middle-aged or old then the changes are only partially reversible (9). To study the possible reversibility of hypertensive vascular changes in man we (10) examined 13 patients and 13 matched controls before and after five years of antihypertensive treatment in the patient group Intraarterial blood pressure and hand blood flow was studied Figure 1 shows the difference in mean blood pressure between patients and controls before and after treatment. This difference is considerably reduced by the therapy (from 46 per cent to 10 per cent). The corresponding difference in resistance at maximal dilatation is also significantly reduced after treatment (from 46 per cent to 14 per cent) These experiments thus indicate that the structural changes in the hand blood vessels are at least partially reversible.

To elucidate this question further we have also studied calf blood flow and indirect arm blood pressure in 54 patients with essential hypertension (WHO stage I II) before and after six months of blood pressure lowering therapy (Figures 2 and 3) Twelve patients have been treated with propranolol or alprenolol and hydrallazine, eighteen with atenolol and twenty-three with mefruside. *Maximal*

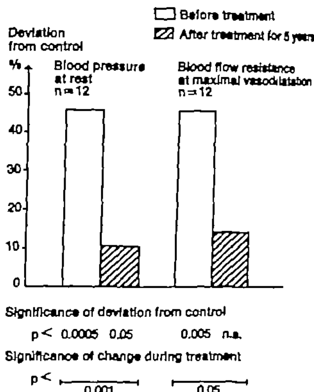


Fig 1 Intra-arterial blood pressure and hand blood flow resistance at maximal vasodilatation expressed as the percent deviation of the hypertensive group from the control group before and after antihypertensive treatment for 5 years.

dilatation was induced by a combination of arterial occlusion in the leg and calf muscle work until exhaustion. Under conditions of vasodilatation none of the drugs changed calf blood flow resistance significantly

There may be several explanations for the discrepancy between the two follow up studies. The duration of treatment is much shorter in the latter one where calf blood flow is examined than in the first one. Furthermore as the calf is exposed to a higher pressure than the hand because of man's upright position the vascular changes in the calf may be of a different nature from those in the hand Like vascular changes in more severe and long standing animal hypertension the vascular changes in the calves of hypertensive patients may show only a limited reversibility (9) because of an extensive collagen invasion in the arteriolar wall.

It can thus be concluded that vascular changes as reflected by blood flow resistance at maximal dilatation in patients with established essential hypertension seem to be partially but not completely reversible on long term blood pressure lowering therapy Regional differences may exist.

Ramon Sivertsson
I do not think so.

Harald Ellasch
We obtained the same results as you when we restudied Varnauskas hypertensive case material from 1955 (Scand. J. Clin. lab. Invest. 1955 suppl. to vol. 7). We found a decrease in cardiac output along with time. (Hypertoni och ateroskleros frågor Saltsjöbadsmötet 1970.)

REFERENCES

1 Folkow B Structural, myogenic, humoral and nervous factors controlling peripheral resistance. In. Hypotensive Drugs ed by M. Harington Pergamon Press, pp 163—174 London 1956.

2. Folkow B Grimby G and Thulesius, O Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance Acta Physiol. Scand. 44 255 1958.

3 Conway J A vascular abnormality in hypertension. A study of blood flow in the forearm. Circulation 27 520 1963

4 Sivertsson R. The haemodynamic importance of structural vascular changes in essential hypertension. Acta Physiol. Scand., Suppl. 343 1 1970

5 Furuyama M Histometrical investigations of arteries in reference to arterial hypertension. Tohoku J Exp Med. 76. 388 1962.

6 Suwa N and Takahashi, T Morphological and Morphometrical Analysis of Circulation in Hypertension and Ischemic Kidney München—Berlin—Wien Urban & Schwarzenberg 1971

7 Lundgren, Y Adaptive changes of cardiovascular design in spontaneous and renal hypertension. Haemodynamic studies in rats. Acta Physiol. Scand., Suppl. 408 1 1974

8 Guyton A. C. Coleman T G Cowley Jr A. W Manning Jr R. D Norman Jr R. A. and Ferguson, J D A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. Circ. Res. 35 159 1974

9 Weiss, L. Aspect of the relation between functional and structural cardiovascular factors in primary hypertension. Experimental studies in spontaneously hypertensive rats. Acta Physiol. Scand. Suppl. 409 1974

10 Sivertsson R and Hansson, L. Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension Clin Sci. & Mol. Med. 51 65 s—68 s, 1976.

DISCUSSION

Lennart Hansson

I would like to ask Per Lund Johansen Have you also re-examined the normal volunteers, whom you had ten years ago and if so did they show the same change in haemodynamics as the hypertensives? Secondly I think it is important, as you stressed that the methods in the first and second study should be identical. Did you in any way check this and if so how did you do it?

Per Lund Johansen

The answer to the first question is that I have so far not studied the normotensive controls. Nevertheless I think that it is possible to draw some conclusions about the differences between the hypertensives and the normotensives. In cross-sectional studies in normotensives, there is a lot of data from USA Canada and I think from Sweden, showing that, as long as the blood pressure is normal, very little actually happens to the cardiac output, the stroke volume and the calculated resistance over the period from 20 up to 45 years of age. But, of course I agree with you that it would have been very interesting if the normotensive subjects had been studied as well.

My answer to your second question is that all patients were out-patients, and they were studied at exactly the same time of day with exactly the same type of equipment, following exactly the same experimental procedure in both the first and the second study

Bengt Pernow

I would like to comment on doctor P Lund-Johansen s findings on cardiac output. In the younger age-groups at least, there was generally found to be a high cardiac index, and it was interesting to see that this high cardiac output ran in parallel to a large oxygen uptake while the arterio-venous oxygen difference was normal. This speaks in favour of a higher metabolic rate in these patients, and obviously they were not what is termed "hyperkinetic I would like to define hyperkinetic circulation as a situation with a low arterio-venous difference. I think that a true hyperkinetic state, which is frequently referred to in literature, is extremely rare in fact, and the reason for the high cardiac output in your cases was, exactly as you suggested that they had a high metabolic rate. Secondly you found when you studied these patients again ten years later that the cardiac index had decreased. I would like to ask you. Was there a decrease in the oxygen uptake at the same time? In other words, was the decrease of the cardiac index due to a decrease in metabolic rate or was it due to structural changes in the heart, changing the heart muscle compliance?

Per Lund-Johansen

I agree with your comments about hyperkinetic circulation and also with your definition of this term. My answer to your second question is that in the youngest age-group the oxygen consumption also decreased at rest. However during muscular exercise there were no significant changes in the oxygen uptake and there was still a decrease in the stroke volume. I therefore think it is possible that the reduction in the stroke volume could have something to do with structural changes in the myocardium, this is speculation of course, but it is in line with results of studies on spontaneously hypertensive rats.

Bengt Scherstén

Is there a critical level of blood pressure which must be passed before structural changes can be expected in the vessels?

Effects of Beta Adrenoceptor Blocking Agents on Haemodynamic Parameters

Lennart Hansson

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Abstract. A review is given of some of the important studies dealing with the haemodynamic effects of beta-adrenoceptor-blockade in the treatment of hypertension.

Emphasis is put on the haemodynamic changes that occur during long-term beta-adrenoceptor blockade and comparisons are made between acute and long-term effects, particularly as regards the change of total peripheral vascular resistance.

As hypertension is a multifactorial disease, one should not expect to find one single mechanism by which the antihypertensive mode of action of beta-adrenoceptor-blocking agents could be explained. However irrespective of whether a humoral or a neurogenic or other possible mechanism is favoured, it is axiomatic that such mechanisms would have to influence blood pressure through changes of either cardiac output or total peripheral vascular resistance (or both). For this reason the haemodynamic changes will always be of importance.

The topic of combined treatment of hypertension using a beta-adrenoceptor-blocking agent in conjunction with a vasodilator and the haemodynamic effects thereof is briefly discussed, and finally some data are presented on the effect of beta-adrenoceptor-blockade on regional haemodynamics.

The clinical usefulness of beta-adrenoceptor blocking agents in the treatment of elevated arterial pressure is well documented (12, 32, 33 42). Following the first clinical reports on the antihypertensive effect of pronethalol (30, 36) and propranolol (31) in 1964 blood pressure lowering effect has been claimed for almost all other agents of this category.

However the mechanism responsible for the reduction in arterial pressure still remains to be fully explained. Since most forms of established hypertension are characterized by a normal cardiac output and an elevated total peripheral vascular resistance (9) and since acute administration of a beta-adrenoceptor blocking agent is known to increase systematic vascular resistance (7 26, 41) the first reports of the antihypertensive effect were surprising.

As blood pressure is a haemodynamic parameter directly dependent on cardiac output and total peripheral vascular resistance it is obvious that any change of blood pressure will have to rely on a change of either cardiac output or total peripheral resistance (or both). For this reason, suggested mechanisms involving factors such as the renin-angiotensin-aldosterone system (3), interference with presynaptic neurons or membrane-stabilizing (local anesthetic) properties of these compounds (5 6) will not be dealt with in detail in this paper since, even if such mechanisms are operable and of practical importance, their final influence on arterial pressure would have to operate through changes of either cardiac output or total peripheral resistance.

This should *not* be understood to mean that one single factor can be excepted to explain the antihypertensive effect of beta-adrenoceptor blocking agents On the contrary as essential hypertension is most probably multifactorial in origin, it should be *expected that* the blood pressure lowering effect of beta-adrenoceptor blocking agents can be obtained through various mechanisms.

HAEMODYNAMIC STUDIES

There is an abundance of haemodynamic studies

Tarazi and Dustan could also demonstrate that the change of mean arterial pressure was significantly correlated to the change of total peripheral resistance but that the change of blood pressure was not correlated to the change of cardiac output (37).

These haemodynamic differences between the acute and longterm effects of beta-adrenoceptor blockade in hypertensive patients have been confirmed by Hansson (11). The re-adjustment of total peripheral vascular resistance that occurs during prolonged treatment is illustrated in Figure 1. That a reduction of cardiac output per se is not sufficient to cause a fall of arterial pressure in the absence of a re-adjustment of total peripheral resistance is illustrated in Figure 2. There "non-responders" who actually showed a 5% increase of mean arterial pressure during prolonged treatment with propranolol had a reduction of cardiac output, which was actually more pronounced than that seen in the "responders". However, total peripheral resistance remained high in the "non-responders" also during prolonged beta-adrenoceptor blockade (11). It should be mentioned that the percentual reduction of stimulated plasma renin activity was of the same order in both groups of patients (14).

It can thus be concluded that a re-adjustment of total peripheral vascular resistance occurs during prolonged beta-adrenoceptor blocking therapy in those hypertensive patients who respond to the treatment. The underlying mechanism for this re-adjustment is still not clarified. A change of baroreceptor activity seems logical and has been suggested (11, 33). However, whether this alteration of baroreceptor mediated vasoconstrictor nerve activity is associated with pre-synaptic beta-adrenoceptor blockade as recently suggested by Langer (22) or whether other metabolic events are of importance remains to be elucidated.

The demonstrated haemodynamic alterations during long-term beta-adrenoceptor blockade are of practical importance. Thus, during the early years of using beta-adrenoceptor blocking agents in the treatment of hypertension, it was often suggested that this kind of treatment should be reserved for individuals with high heart rates or high cardiac outputs. This seemingly logical approach—logical in view of the evident and easily demonstrated cardiac effects of these agents—cannot be justified after an analysis of available data. Thus, there is no correlation between pre-treatment levels of heart rate or cardiac output and blood pressure reduction obtained during beta-adrenoceptor blockade (2, 15, 37). Even patients showing marked tachycardia and marked elevation of cardiac output do not invariably show a reduction of their elevated arterial pressure in spite of the fact that tachycardia and elevated cardiac output could be controlled by beta-adrenoceptor blockade (17).

It can thus further be concluded that the presence of high heart rate or high cardiac output (hyperkinetic circulation) in the pre-treatment situation will not per se guarantee that blood pressure will be controlled when a beta-adrenoceptor blocking agent is administered.

On the other hand it may be argued that beta-adrenoceptor blockade instituted in the early phase of hypertension—when cardiac participation supposedly is of great importance (19, 20)—seems to be effective in preventing a rise of blood pressure in spontaneously hypertensive rats, whereas no effect could be demonstrated when this treatment was given during later stages (8). However also in this situation objections could be raised. Thus, it has been shown that propranolol cannot prevent development of hypertension during electrical stimulation of the stellate ganglion in conscious dogs, indicating that "cardiogenic" hypertension may develop in the presence of beta-adrenoceptor blockade (23).

Recent haemodynamic studies

During the last few years a number of studies have been published, which deal with haemodynamics in hypertensive patients before and during treatment with various beta-adrenoceptor blocking agents. Of great interest are the studies made by Lund-Johansen, who has studied a number of beta-adrenoceptor blocking agents and their effect on haemodynamic parameters, during rest and physical exercise. Usually these studies have been performed before and following one year of treatment with the respective drugs. In a comparison of alprenolol, atenolol, metoprolol and timolol statistically significant reduction of mean arterial pressure (11—18%) was found with all the above agents. Heart rate was also significantly reduced in all groups in this study. However due

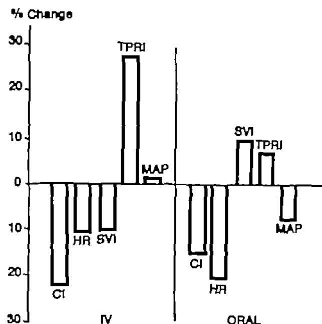


Fig 1 Changes of haemodynamic parameters following acute and prolonged beta-adrenoceptor blockade with propranolol in hypertensive patients. CI=Cardiac Index HR=Heart rate MAP=Mean Arterial Pressure TPRI=Total Peripheral Resistance index.

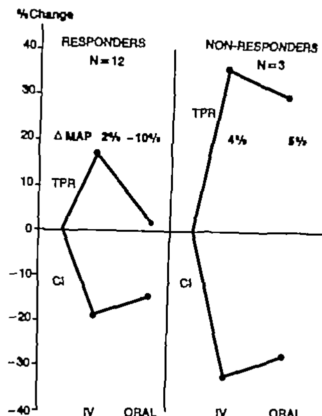


Fig 2 Changes of haemodynamic parameters in 12 patients showing a reduction of blood pressure and 3 patients showing no reduction of blood pressure during prolonged treatment with propranolol. CI=Cardiac Index, MAP=Mean Arterial Pressure, TPRI=Total Peripheral Resistance index.

with several different beta-adrenoceptor blocking agents in the literature. It is beyond the scope of this paper to cover them all. However a few selected papers which have contributed to our understanding of the haemodynamics of these agents will be reveiwed. The haemodynamic studies with beta-adrenoceptor blocking agents in hypertensive patients performed at the Cleveland Clinic Research Division are undoubtedly of prime interest in this respect. Thus, in 1968 Ulrych et al published reports on acute intravenous administration of propranolol to normotensive and hypertensive subjects (41) A significant reduction of cardiac output was demonstrated. However due to a compensatory increase of calculated total peripheral vascular resistance the mean arterial blood pressure did not change (41) This finding was not surprising in view of previous results with acute administration of a beta-adrenoceptor blocking agent. However the Cleveland Clinic group at the same time published reports on the long-term effects of beta-adrenoceptor blockade in a small number of hypertensive patients (10) In this study they reported the "paradoxical" finding that blood pressure was decreased in spite of a chronic reduction of cardiac output.

Tarazi and Dustan have later demonstrated the striking difference between the acute and chronic haemodynamic effects of beta-adrenoceptor blockade in hypertension. Following acute administration of propranolol, they confirmed earlier observations that heart rate and cardiac output were reduced significantly but due to a compensatory increase of total peripheral vascular resistance blood pressure did not change in this situation. However during repeated haemodynamic examinations in the same patients a significant reduction of mean arterial blood pressure was found due to the fact that total peripheral resistance was readjusted down to the initial level in the presence of a maintained reduction of cardiac output (37)

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to differences in stroke volume total peripheral resistance did not change uniformly Thus, in the timolol group total peripheral resistance at rest remained significantly elevated after one year whereas this parameter was "normalized" during treatment with alprenolol atenolol and metoprolol (24)

Studies with pindolol before and after 8 weeks of treatment have also demonstrated that statistically significant reductions of systemic arterial pressure are obtained (1) In agreement with other studies significant reductions of heart rate and cardiac output were observed, whereas no significant changes of stroke volume or total peripheral resistance were seen (1).

Combined treatment with vasodilators

As most forms of established hypertension are characterized by normal cardiac output and elevated peripheral resistance (9) a vasodilator would appear as the most logical remedy However due to compensatory mechanisms elicited through the baroreflex mechanism treatment with a vasodilator as the sole agent is rarely successful. Clearly the combined use of a vasodilator and a beta adrenoceptor blocking agent would appear to solve the problem of reflexogenic increase of sympathetic tone particularly as regards stimulation of the heart. Several clinical applications of such combinations have also proved to be useful (13 21 35) The haemodynamic value of adding a beta adrenoceptor blocking agent to a vasodilator drug therapy has been demonstrated e g. as regards alprenolol and dihydrallazine (35) or tolamolol and prazosin (25)

The additional reduction of blood pressure when a beta adrenoceptor blocking agent is added to a vasodilator drug regime has been claimed to be dependent on a renin suppressing action of the beta adrenoceptor blocker in this situation (29). However others have not been able to establish a correlation between the humoral and haemodynamic changes during combined therapy (38).

Regional haemodynamics

It is easy to overlook the fact that total peripheral vascular resistance is a calculated parameter depending on the exact measurements of arterial pressure and cardiac output. Total peripheral resistance thus reflects the sum of resistance patterns in all vascular beds of the body Clearly directionally opposite changes of resistance may occur in different vascular beds, the effects of which will eliminate themselves as regards influence on total peripheral resistance. Unfortunately few vascular beds have been studied during the influence of beta-adrenoceptor blocking agents.

As regards cerebral blood flow it has been shown in monkeys that cerebral blood flow is relatively less reduced than blood flow in other vascular beds (27) The effect of pindolol on forearm blood flow (mainly a muscle vascular bed) shows no reduction of blood flow and no change of resistance at rest. However during physical exercise a significant reduction of forearm resistance was found (1) Similar studies with propranolol and atenolol show significant reductions of systemic arterial pressure but also significant reductions of blood flow at rest in the calfs (mainly a muscle vascular bed) (16) The reduction of blood flow to the legs during exercise and rest due to treatment with propanolol has been found to be directly related to a reduction of arterial pressure and thus resistance in this vascular beds does not increase during chronic beta-adrenoceptor blockade (39 40) This is in agreement with studies in rats showing a reduction of muscle blood flow (28). Moreover it has been reported that glomerular filtration rate is decreased in hypertensive patients during long term beta-adrenoceptor blockade (18), although this finding has not been seen in all patients by other investigators (38) Liver blood flow has been found to fall more than would correspond to the reduction in systemic arterial pressure during prolonged beta-adrenoceptor blockade thus indicating an increase of vascular resistance in the liver (4, 39) This reduction of blood flow to the liver could have implications for the metabolism of some of the beta-adrenoceptor blocking agents themselves.

REFERENCES

1 Atterhog, J-H. Dunér H. & Pernow B Hemodynamic effect of pindolol in essential hypertension with special reference to resistance and capacitance vessels of the forearm. Acta Med Scand. 190: 251 1976.

2. Birkenhager W H., Kraus, X. H Schalekamp,

M. A. D. H., Kolsters, G & Kroon, B. A. M.. Antihypertensive effect of propranolol. Folia Med. Neerl. 14 67 1971
3 Bühler F R., Laragh, J H. Baer L., Darracott Vaughan, E. & Brunner H. R.. Propanolol inhibition of renin secretion. New Engl. J Med. 287 1209 1972.
4 Christensen, N. J., Trap-Jensen, J Clausen, J P Noer I Krogsgaard, A. R. & Andrée Larsen O Effect of beta-receptor blockade on heart rate hepatic blood flow and circulating noradrenaline during exercise in man. Acta Physiol. Scand 95 42 A, 1975
5 Day M. D & Roach, A. G.. Beta adrenergic receptors in the central nervous system of the cat concerned ith control of arterial blood pressure and heart rate. Nature 242: 30, 1973
6 Elash, S & Weinstock, M Role of adrenergic neurone blockade in the hypertensive action of propranolol. Brit. J Pharmacol. 43 287 1971
7 Epstein, S. E. & Braunwald, E.. Beta-adrenergic receptor blocking drugs: Mechanisms of action and clinical applications. New Engl. J Med. 275 1106, 1966.
8. Folkow B., Lundgren, Y & Weiss, L.. The effect of prolonged propranolol treatment on blood pressure and structural design of the resistance of vessels in young spontaneously hypertensive rats (SHR) Acta Physiol Scand. 84 8 A, 1972.
9 Freis, E. D Hemodynamics in hypertension Phys. Rev 40 27 1960.
10. Frohlich, E. D Tarazi, R. C., Dustan, H. P & Page, I. H.. The paradox of beta-adrenergic blockade in hypertension. Circulation 37 417 1968.
11 Hansson, L. Beta-adrenergic blockade in essential hypertension Effects of propranolol on hemodynamic parameters and plasma renin activity Acta Med Scand suppl 550, 1973
12. Hansson, L Malmcrona, R Olander R Rosenhall, L Westerlund A., Aberg, H & Hood, B Propranolol in hypertension Report on 158 patients treated up to one year Klin Wschr 40-364, 1972
13 Hansson, L Olander R. Malmcrona, R. & Westerlund, A Treatment of hypertension with propranolol and hydralazine. Acta Med. Scand 190. 531 1971
14 Hansson L Z eifler A J Julius, S & Hunyor S N Hemodynamic effects of acute and prolonged beta-adrenergic blockade essential hypertension. Acta Med Scand 195 549 1974
15 Hansson L Z eifler A J Julius, S & Ellis, C N Propranolol therapy in essential hypertension. Observations on predictability of therapeutic response Int J Clin Pharmacol 10 79 1974
16 Hansson, L & Sivertsson, R Regional hemodynamic effects of propranolol and atenolol in hypertensive patients (T be published)
17 Ibrahim, M M Tarazi, R C Dustan, H. P Bravo E L & Gifford, R W Jr Hyperkinetic heart in severe hypertension A separate hemodynamic entity Amer J Cardiol. 35 667 1975.
18 Ibsen H. & Sederberg-Olsen, P Changes in glomerular filtration rate during long-term treatment with propranolol in patients with arterial hypertension. Clin. Sci. Mol Med. 44 129 1973
19 Julius, S. & Con ay J Hemodynamic studies in patients ith borderline blood pressure elevation. Circulation 38, 282, 1968.
20 Julius, S., Randall, O S., Esler M D Kashima, T Ellis, C. N & Bennet, J Altered cardiac responsiveness and regulation in the normal cardiac output type of borderline hypertension. Circulation Res., suppl 1 36. 399, 1975
21 Katila M. & Frick, M. H.. Combined dihydralazine and propranolol in the treatment of hypertension Int. J Clin Pharmacol 4 111 1970.
22. Langer S. Z.. The role of alpha and beta presynaptic receptors in the regulation of noradrenaline release elicited by nerv stimulation. Clin. Sci. Mol. Med. (In press), 1976
23 Liard, J F Tarazi R C. Ferrario C. M & Manger W M., Hemodynamic and humoral characteristics of hypertension induced by prolonged stellate stimulation in concious dogs. Circulation Res. 36. 455 1975
24 Lund-Johansen, P & Ohm, O J Hemodynamic long-term effects of beta-receptor blocking gents in hypertension. A comparison between alprenolol, atenolol, metoprolol and timolol Clin. Sci. Mol. Med. 51 suppl. 3 481 1976.
25. Lund-Johansen, P Hemodynamic long-term effects of prazosin plus tolamolol in essential hypertension (T be published).
26 Lucchesi, B R. & Whitsitt, L. S. The pharmacology of beta-adrenergic blocking gents Progr Cardiovas. Dis. 11 410 1969
27 Nies, A. S Evans, G H. & Shand, D G Regional hemodynamic effects of beta-adrenergic blockade with propranolol in the unanesthetized primate Amer Heart J 85 97 1973
28. Nishiyama, K. Nishiyama, A Pfeffer M. A. & Frohlich, E D Systemic and regional flow distribution in normotensive (WKY) and spontaneously hypertensive (SHR) young rats with prolonged beta-adrenergic blockade. Fed. Proc. 34 399 1975
29 Pettinger W A & Mitchell, H C Renin release saralasin and the vasodilator beta-blocker drug interaction in man New Engl J Med. 292: 1214 1975
30. Prichard, B. N C.. Hypotensive action of pronethalol Brit. Med J 1 1227 1964
31 Prichard B. N C & Gillam, P M. S.. The use of propranolol in the treatment of hypertension. Brit Med J 11 725 1964
32 Prichard, B N C. & Gillam P M. S.. Propranolol in hypertension. Amer J Cardiol. 18 387 1966.
33 Prichard, B N C. & Gillam, P M. S Treatment of hypertension ith propranolol. Brit. Med. J 1 7 1969

34 Sannerstedt R., Stenberg, J Vedin A. Wilhelmsson C. & Werkö L. Chronic beta-adrenergic blockade in arterial hypertension. Hemodynamic influences of dihydrallazine and dynamic exercise and clinical effects of combined treatment. Amer J Cardiol. 29 718 1972.

35 Sannerstedt R. Selection of hypertensive patients for treatment with beta-blockers alone or in combination In. Beta-Blockers: Present status and future prospects. Ed W Schweitzer Hans Huber Basle 1975

36. Schröder G & Werkö L. Nethalide a beta-adrenergic blocking agent. Clin. Pharmacol. Ther 5 159 1964

37 Tarazi R. C. & Dustan H P Beta-adrenergic blockade in hypertension Practical and theoretical implications of long-term hemodynamic variation. Amer J Cardiol. 29 633 1972.

38 Tarazi R. C. Dustan, H P & Bravo E. L. Hemodynamic effects of propranolol in hypertension a review Postgrad. Med. J., suppl. 4 52. 92, 1976

39 Trap-Jensen J., Clausen, J P Noer L, Mogensen, A Christensen N J Krogsgaard, A R & Larsen O A Regional hemodynamic changes during exercise in essential hypertension before and after prolonged beta-receptor blockade. Scand J Clin Lab. Invest. 35 suppl. 143. 60 1975.

40. Trap-Jensen, J., Clausen, J P., Noer L, Larsen O A. Krogsgaard, A. R & Christensen, N. J. The effects of beta-adrenoceptor blockers on cardiac output liver blood flow and skeletal muscle blood flow in hypertensive patients. Acta Physiol. Scand. 98 suppl. 440 30, 1976.

41 Ulrych, M Frohlich, E. D Dustan, H. P & Page I H Immediated hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation 37 411 1968

42. Zacharias F J Cowen, K J Prestt, J Vickers J & Wall, B. G.. Propranolol in hypertension A study of long term therapy 1964—1970. Amer Heart J 83 755 1972.

Haemodynamic effects of pindolol in hypertensive patients

Jan-Henrik Atterhög, Hans Dunér
and Bengt Pernow

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and the Department of Medicine Sabbatsbergs Hospital
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Abstract. Five men and five women, mean age 48 years, with hypertension in stages I or II of the WHO classification, were given peroral treatment with pindolol.

The pindolol treatment lead to a significant decrease in the systolic and diastolic blood pressure, at rest and during work both after 2 months and after 16 months treatment.

Three mechanisms seem to be involved in the antihypertensive effect of pindolol: 1) a negative chronotropic effect on the heart, 2) a decrease in peripheral vascular resistance and 3) an increase in venous capacitance affecting the venous return.

Comparison of the results after 2 and after 16 months of treatment suggests that a decrease in cardiac output is an early mechanism in the lowering of the blood pressure, while a decrease in vascular resistance seems to be more important after long-term treatment with pindolol.

Although beta-adrenoreceptor blocking agents have been widely used in the treatment of hypertension for more than ten years, the mechanisms by which the antihypertensive action is achieved are not yet fully explained. This is probably partly due to the fact that a uniform mode of action of betablockers does not exist in the multifactorial disease which essential hypertension constitutes. Furthermore it has been repeatedly shown, that betablockers influence both cardiac output and total peripheral resistance, the two haemodynamic variables mainly responsible for the blood pressure level. In addition, the effect of the betablocking agents on haemodynamics is entirely dependent on the pharmacological characteristics of the particular preparation, including degree of selectivity intrinsic activity and quinidine-like effect.

Pindolol (Visken® Sandoz) is a potent beta-adrenoceptor blocking agent with a weak quinidine-like efect, a receptor stimulating activity but no effect on alpha-adrenergic receptors. The hypotensive effect of pindolol is well documented (2, 8 10, 12).

MATERIAL AND PROCEDURE

The material consists of ten patients, 5 women and 5 men with essential hypertension (stage I and II according to the WHO classification). The mean age of the patients was 47.8 years (range 31—61) at the start of the study. The blood pressure criteria for hypertension was a systolic pressure of not less than 1 5 mm Hg and a diastolic pressure not less than 105 mm Hg. Patients with substantial disorders in addition to hypertension such as latent or manifest cardiac insufficiency bronchial asthma, renal insufficiency or diabetes, were excluded. No signs of organic cardiovascular changes were present in eight of the patients (stage I); the other two had a slightly enlarged heart volume but no other signs of cardiovascular changes (stage II).

At the start of the study none of the patients had any hypotensive medication. The initial blood pressure measurements, confirming the diagnosis of hypertension in the individual case, were made on three occasions separated by intervals of about one week. The blood pressure was measured indirectly on the left upper arm after 5 min rest in the supine position. Thereafter a run-in placebo period of 4 weeks duration started with a blood pressure recording after 2 and 4 weeks. The placebo period ended with a haemodynamic examina-

34 Sannerstedt R. Stenberg, J Vedin, A. Wilhelmsson C. & Werkö L. Chronic beta-adrenergic blockade in arterial hypertension. Hemodynamic influences of dihydrallazine and dynamic exercise and clinical effects of combined treatment Amer J Cardiol. 29 718 1972.

35 Sannerstedt R. Selection of hypertensive patients for treatment with beta-blockers alone or in combination. In Beta Blockers: Present status and future prospects. Ed. W Schweitzer Hans Huber Basle 1975

36. Schröder G & Werkö L. Nethalide, a beta-adrenergic blocking agent Clin. Pharmacol Ther 5 159 1964

37 Tarazi R. C. & Dustan H P Beta-adrenergic blockade in hypertension Practical and theoretical implications of long-term hemodynamic variation Amer J Cardiol. 29 633 1972.

38 Tarazi R C., Dustan H P & Bravo E. L. Hemodynamic effects of propranolol in hypertension a review Postgrad Med J suppl. 4 52 92, 1976.

39 Trap-Jensen, J Clausen, J P., Noer I Mogensen A Christensen N J., Krogsgaard, A. R. & Larsen O A. Regional hemodynamic changes during exercise in essential hypertension before and after prolonged beta-receptor blockade Scand. J Clin. Lab Invest 35 suppl 143 60 1975

40 Trap-Jensen, J Clausen J P Noer I, Larsen O A Krogsgaard A R. & Christensen, N J The effects of beta-adrenoceptor blockers on cardiac output liver blood flow and skeletal muscle blood flow in hypertensive patients. Acta Physiol. Scand 95 suppl. 440 30 1976.

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		Control	2 months	16 months	Diff 2—16 months
Mean arterial blood pressure mm Hg	Rest	140	—23	—27*	
	Exercise	159	—29*	—33**	
	After exercise	134	—21	—23	
Heart rate beats/min	Rest	74	— 8*	— 7*	
	Exercise	119	—18**	—18*	
	After exercise	84	— 9*	— 7*	
Cardiac output l/min	Rest	5.5	— 0.7*	— 0.4	
	Exercise	10.4	— 1.4**	— 0.4	
	After exercise	6.1	— 0.3	± 0	
Stroke volume ml	Rest	75	— 1	1	
	Exercise	89	± 0	11	
	After exercise	76	2	3	
Systemic vasc. resistance arb units	Rest	27	— 2	— 3*	
	Exercise	16	— 1	— 3***	**
	After exercise	23	— 3	— 5	
Forearm blood flow ml/100 ml/min	Rest	2.8	0.1	0.4	
	Exercise	2.8	— 0.2	0.9	
	After exercise	3.6	± 0	0.6	
Forearm vasc. resistance arb units	Rest	60	—14	—24	
	Exercise	65	14	—30*	
	After exercise	45	—10	—16	
Venous tone mm Hg/ml × 100 ml	Rest	3.0	— 1.0*	— 0.7	
	Exercise	2.9	— 0.9*	— 1.1	
	After exercise	3.3	— 1.5	— 1.8	

Table 1. Central hemodynamics and peripheral circulatory data at rest, during and 4 min after exercise before (control) and after 2 months and 16 months on pindolol. The levels of significance of the changes after 2 months and 16 months compared to the control examination and the difference between the situation after 16 months compared to 2 months are illustrated as [illegible] and ** ($p<0.05$, $p<0.01$ and $p<0.001$ respectively).

bo treatment and somewhat, although not significantly lower than those recorded after 2 months of treatment. Also the pressures recorded during and after exercise were significantly ($p<0.001$) lower than in the control study. Heart rate was lower most strikingly during exercise ($p<0.01$). Cardiac output was slightly lower but the difference from the control was not significant. Stroke volume was significantly higher during exercise ($p<0.05$). The most striking circulatory effect after 16 months of treatment was the decrease in systemic and forearm vascular resistance before, during and after exercise. Venous tone was still lower than in the control study.

Differences between 2 and 16 months of treatment
The systolic, diastolic and mean arterial blood pressure were numerically lower after 16 months of pindolol treatment than after 2 months but the values obtained were not significantly lower. Heart rate was unchanged. Cardiac output and stroke volume were somewhat higher, the differences,

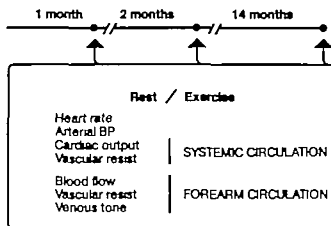


Fig 1 Variables studied.

tion at rest and during exercise. After this examination, treatment with pindolol was started at a dose of 10 mg twice daily The blood pressure was checked after 1 and 3 weeks of treatment, if the diastolic pressure had not fallen at least 20 mm Hg or if the blood pressure exceeded 160/95 the dose was increased to 15 mg twice daily and again after a further 3 weeks to 20 mg twice daily if the blood pressure had not fallen as indicated above. In this way the desired decrease in blood pressure was achieved in one patient with 20 mg in four patients with 30 mg and in five patients with 40 mg of pindolol daily The haemodynamic examination was then repeated after a mean duration of treatment of 8 weeks (range 6—11) and after a further 60 (range 52—73) weeks period of treatment.

The haemodynamic examinations were performed in the morning. The patient had taken his ordinary pindolol dosage 2 hours before examination but was otherwise fasting. The analyses were made with the patient in the supine position at rest as well as during and 4 min after an exercise on a bicycle ergometer The variables studied and the procedure are shown in Figures 1 and 2. For further details see ref (1).

Table 1 summarizes the results obtained after 2 months of pindolol treatment (1) and also includes results after 16 months of treatment (full data to be published in Acta med Scand., 1977) Statistical significance of differences was evaluated by t-tests on paired observations.

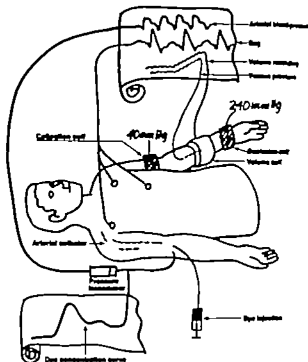


Fig 2 Schematic illustration of the procedure used at the haemodynamic examination.

RESULTS

Effect of 2 months of treatment

The decrease in systolic, diastolic and mean arterial blood pressure was highly significant ($p<0.001$) both at rest and during exercise. Heart rate was significantly lower at rest ($p<0.01$), during exercise ($p<0.01$) and after exercise ($p<0.05$) as compared to the control situation during placebo treatment Cardiac output was significantly decreased which was most accentuated during exercise ($p<0.01$), while stroke volume was unchanged No effect was noticed on calculated systemic vascular resistance at rest or during exercise, while a slight decrease ($p<0.05$) was found after exercise. Peripheral resistance in the forearm decreased significantly during exercise ($p<0.05$) Venous tone was decreased before ($p<0.05$), during ($p<0.01$) and after ($p<0.05$) exercise

Effect of 16 months of treatment

After 16 months of treatment with pindolol the mean values of the systolic and diastolic arterial blood pressure at rest were 153±14 and 85±12 mm Hg respectively These values are significantly ($p<0.001$) lower than those recorded during place

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	Exercise	16	— 1	— 3**	**
	After exercise	23	— 3	— 5**	
Forearm blood flow ml/100 ml/min	Rest	2.8	0.1	0.4	
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The systolic, diastolic and mean arterial blood pressure were numerically lower after 16 months of pindolol treatment than after 2 months but the values obtained were not significantly lower. Heart rate was unchanged. Cardiac output and stroke volume were somewhat higher, the differences,

however being significant ($p<0.05$) only during exercise. Systemic and forearm vascular resistance were lower and forearm blood flow higher after 16 months of treatment, the difference being significant ($p<0.05$) during exercise. No difference was found in venous tone.

DISCUSSION

When studying the effect of hypotensive drugs it is important to prolong the observation time and make repeated analyses of the haemodynamic changes to compare with the control situation. This is obvious from the present results which show that although the hypotensive effect of the drug was maintained over a long period of time (in the study 16 months) the mechanisms behind the hypotensive effect changed during the period of treatment. The level of blood pressure is roughly speaking a function of cardiac output and peripheral vascular resistance. Early after the onset of treatment the hypotensive effect was entirely due to a negative chronotropic effect on the heart with unchanged stroke volume lowering the cardiac output with only a small decrease of or no effect on the peripheral resistance. Later on the pressure lowering mechanism was changed to a dominant effect on the periphery while cardiac output was almost normalized, the arterial blood pressure being kept at an unchanged low level. It is tempting to suggest that this gradual decrease in peripheral resistance is due to a partial reversal of structural changes in the resistance vessels as discussed earlier at this symposium. This suggestion is in conformity with findings in spontaneously hypertensive rats that betablockers are able to reduce to some extent already established structural changes (15).

However the picture is complicated by the fact that not all reports on long term studies on the effect of betablockers are in conformity with our findings. Thus Lund-Johansen found that prolonged treatment with alprenolol (5) timolol (6) and atenolol (7) did not decrease peripheral resistance. Similarly Trap-Jensen (1976) recently reported that the hypotensive effect of propranolol was still after one year entirely due to a decrease in cardiac output while peripheral resistance was unchanged. On the other hand Koch (4) found that labetalol (AH 5158) a combined alpha and beta-adrenoceptor blocking agent gave a decreased peripheral resistance which conforms with our results on pindolol. These different results are probably due to the fact that the studies have been performed with betablocking agents having different degree of specificity intrinsic activity anaesthetic activity etc. and stress the importance of a careful haemodynamic analysis of each individual preparation of this kind.

The majority of studies on the antihypertensive effects of betablocking agents deal merely with the situation at rest. However analysis of the haemodynamic events during and after physical exercise add valuable information on the effect of the antihypertensive treatment. It is important to determine whether the hypotensive effect obtained at rest is maintained during physical work similar to that in which the patient is engaged in daily life. As is evident from the present study the effect of pindolol after two months of treatment was even more pronounced during exercise than at rest for some important variables such as heart rate cardiac output, forearm vascular resistance and venous tone. The same was true after 16 months of treatment.

Venous tone of the deep forearm was found to be significantly lower during pindolol administration as compared to the control situation. Earlier Walsh et al. (14) have found reduced venous distensibility in hypertensive patients, which was normalized by various antihypertensive drugs such as chlorothiazides, reserpine and methyldopa. Studies in animals confirm these findings. Thus Overbeck (9) observed a shift of the venous pressure-volume relation towards the pressure axis in experimentally induced renal hypertension in the dog. Similarly Simon (11) recently found a decreased venous capacity in the spontaneously hypertensive rat. If this reduction in venous compliance is a result of a neurogenic vascular influence or an increased water content of the venous wall is not yet definitely settled. If however the increased venous tone in hypertensive patients is due to an increased venomotor activity as postulated by Walsh et al. (14) this is probably mediated by alpha-receptors (3). Since no basis for an alpha-adrenergic blocking action of pindolol has hitherto been demonstrated the mechanism by which pindolol decreased venous tone in the present cases of essential hypertension is not clear. The effect might be due either to the intrinsic

activity of pindolol or an effect on the central nervous system.

REFERENCES

1 Atterhög, J.-H., Dunér H, & Pernow B Hemodynamic effect of pindolol in essential hypertension with special reference to the resistance and capacitance vessels of the forearm. Acta med. Scand. 199 251 1976.
2 Dunér H., The effect of LB 46 on the blood pressure in essential hypertension Indian Heart J 24 236, suppl. 1 1972.
3 Johansson, B. & Ljung, B., Sympathetic control of rhythmically active vascular smooth muscle as studied by a nerve-muscle preparation of portal vein Acta physiol. scand. 70: 299 1967
4 Koch, G Hemodynamics of the lung- and systemic circulation after long-term treatment with combined alpha- and betareceptor blocking agent in essential hypertension. Proc. Swedish Med. Assoc. Meeting, p. 86, 1976.
5 Lund-Johansen, P Hemodynamic changes t rest and during exercise in long-term beta-blocker therapy of essential hypertension. Acta med. Scand 195 117 1974
6 Lund-Johansen, P Hemodynamic long-term effects of timolol at rest and during exercise in essential hypertension, Acta med. Scand. 199 263 1976
7 Lund-Johansen P Haemodynamic long-term effects of new β-adrenoceptor blocking drug, atenolol (ICI 66082), in essential hypertension, Br J clin Pharmacol. 3 445, 1976.
8 Morgan, T O Louis, W J Dawborn, J K & Doyle A. E The use of prindolol (Visken) in the treatment of hypertension. Med. J Aust. 59 309 1972
9 Overbeck, H W Hemodynamics of early experimental renal hypertension in dogs. Normal limb blood flow elev ted limb vascular resistance and decreased venous compliance. Circulat. Res. 31 453 1972
10 Seedat Y K. & Stewart Wynne E. Clinical experiences ith prindolol (Visken) in the therapy of hypertension. S Afr med J 46 124 1972.
11 Simon, G Altered enous function in hypertensive rats Circulat Res 38 412, 1976.
12 Simpson, S O & Waal-Manning, H. J Hypertension and beta-adrenergic blockade. In: New Horizons in Medicine (1) Symposium. Beta Adrenergic Blocking Agents, Sandoz, Sydney 1970
13 Trap-Jensen, J Clausen, J P Hartling, O Krogsgaard A R & Noer I Central and peripheral circulation in patients ith hypertension treated ith Propranolol and Hydralazin. Proc. Swedish Med Assoc Meeting, p. 181 1976.
14 Wahls, J A Hyman C & Maronde R, F Venous distensibility in essential hypertension. Cardiovasc Res. 3 338 1969
15 Weiss, L. Aspects of the relation between functional and structural cardiovascular factors in primary hypertension. Experimental studies in spontaneously hypertensiv rats. Acta physiol. scand. suppl. 409 1974

DISCUSSION

Olav Thulesius

Increased vascular reactivity to vasoconstrictor stimuli has been considered to be an important mechanism in the pathogenesis of essential hypertension. This is believed to be connected with an increased sensitivity of the vascular smooth muscle cells to physiological stimulation, e.g. with the neurotransmitter noradrenaline. Another possible explanation may be altered geometrical proportions of the vascular wall, with an increased wall/lumen ratio, a mechanism, which in itself for purely anatomical reasons, gives rise to an altered vascular response pattern with increased vasoconstriction, with normal adrenoceptor stimulation.

In the Department of Clinical Physiology and Surgery of Växjö Central Hospital, Jan-Erik Gjöres, Erik Berlin and I undertook a study to test these hypotheses.)

Arterial biopsies were obtained in abdominal surgery on 11 hypertensive and 21 normotensive subjects. The hypertensive subjects had mild to moderate essential hypertension and only 7 of them were being treated with antihypertensive drugs. Treatment was interrupted prior to the operations.

The arterial biopsies were immediately put into chilled Kreb solution and then cut into helical strips Thereafter they were suspended between a clamp and transducer permitting the recording of isometric tension. The organ bath was continuously aerated with 95% oxygen and 5% carbon dioxide and temperature was kept at 37 C

Each strip was equilibrated for two hours. Noradrenaline was then administered.

Values of threshold and maximal contraction are plotted as a *function* of blood pressure in Figures 1 and 2. From these it can be seen that the threshold values for noradrenaline are almost identical for *all* the subjects tested. The same holds for ED_{50} and the force of maximal concentration. A regression analysis of systolic blood pressure versus maximal tension showed slight correlation of maximal tension to increasing arterial blood pressure. It is possible that this correlation might be more pronounced if further patients with higher pressure could be included in the material.

The present results do not lend support to the assumption that arterial strips from patients with essential hypertension are more responsive to the

) This study was supported by grant from Tore Nilsson fond

however being significant (p<0 05) only during exercise Systemic and forearm vascular resistance were lower and forearm blood flow higher after 16 months of treatment the difference being significant (p<0 05) during exercise No difference was found in venous tone

DISCUSSION

When studying the effect of hypotensive drugs it is important to prolong the observation time and make repeated analyses of the haemodynamic changes to compare with the control situation. This is obvious from the present results which show that although the hypotensive effect of the drug was maintained over a long period of time (in the study 16 months) the mechanisms behind the hypotensive effect changed during the period of treatment. The level of blood pressure is roughly speaking a function of cardiac output and peripheral vascular resistance. Early after the onset of treatment the hypotensive effect was entirely due to a negative chronotropic effect on the heart with unchanged stroke volume lowering the cardiac output with only a small decrease of or no effect on the peripheral resistance. Later on the pressure lowering mechanism was changed to a dominant effect on the periphery while cardiac output was almost normalized the arterial blood pressure being kept at an unchanged low level. It is tempting to suggest that this gradual decrease in peripheral resistance is due to a partial reversal of structural changes in the resistance vessels as discussed earlier at this symposium. This suggestion is in conformity with findings in spontaneously hypertensive rats that betablockers are able to reduce to some extent already established structural changes (15)

However the picture is complicated by the fact that not all reports on long term studies on the effect of betablockers are in conformity with our findings. Thus Lund-Johansen found that prolonged treatment with alprenolol (5) timolol (6) and atenolol (7) did not decrease peripheral resistance. Similarly Trap-Jensen (1976) recently reported that the hypotensive effect of propranolol was still after one year entirely due to a decrease in cardiac output while peripheral resistance was unchanged On the other hand Koch (4) found that labetalol (AH 5158) a combined alpha and beta-adrenoceptor blocking agent gave a decreased peripheral resistance which conforms w our results on pindolol. These different results probably due to the fact that the studies h been performed with betablocking agents hav different degree of specificity intrinsic activ anaesthetic activity etc. and stress the importa of a careful haemodynamic analysis of each in ividual preparation of this kind

The majority of studies on the antihypertensi effects of betablocking agents deal merely w the situation at rest. However analysis of t haemodynamic events during and after physic exercise add valuable information on the effe of the antihypertensive treatment. It is importa to determine whether the hypotensive effect o tained at rest is maintained during physical wo similar to that in which the patient is engaged daily life. As is evident from the present stud the effect of pindolol after two months of trea ment was even more pronounced during exerci than at rest for some important variables such heart rate, cardiac output, forearm vascular r sistance and venous tone. The same was true aft 16 months of treatment.

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was carried out on patients with coronary insufficiency

Eight men age 43—57 with severe angina pectoris, pathological ECG-reactions in work tests and low maximal working capacity were catheterized. Arterial blood pressure and heart frequency were registered in the supine position at rest and during work and cardiac output was determined according to Fick's principle. After 30 minutes rest, pindolol 0.014 mg/kg body weight was given intravenously and the examination procedure was repeated after a further 30 minutes.

The mean systolic blood pressure decreased during work ($p<0.05$) as a result of a decreased cardiac output ($p<0.05$) while the peripheral vascular resistance was unchanged (Figure 1). The decrease of the cardiac output was mainly due to a lowered heart rate ($p<0.01$) while stroke volume increased ($p<0.01$) (Figure 2).

In conclusion, pindolol had an effect, in this trial, which was more like that of selective betablockers than non-selective ones.

Torbjörn Lundman

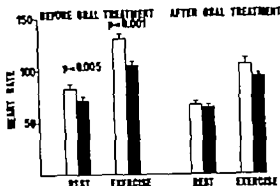
We have measured the acute effect of propranolol before and after long-term oral treatment, in a trial performed at the Serafimer Hospital with Brundin and Edhag *(Br Heart J Vol 38 1065—1072, 1976)*

Eight patients with moderate hypertension were studied I hospital, first haemodynamic study was done before treatment The patients were then given propranolol and after long-term treatment (2—9 months), they were taken into hospital again and propranolol was withdrawn for three days That *time is enough for the drug to disappear from the* blood and also for the metabolites to disappear from the blood and from the heart tissue.

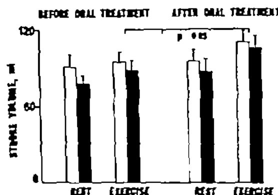
The haemodynamic measurements were done first at rest, then during exercise Following a short pause new basal measurements were performed Then propranolol was infused in a dose of 0 2 mg/kg body weight After fiv minutes new measurements were performed at rest and during exercise Pressures were recorded in the right heart, in the subclavian artery and the cardiac output was measured *with the Fick principle*

Figure 1 shows the results for heart rate There is a significant reduction of *heart rate after intra*venous propranolol both during rest and during exercise But after the long-term treatment, propranolol injection did not significantly reduce heart rate either t rest or during exercise

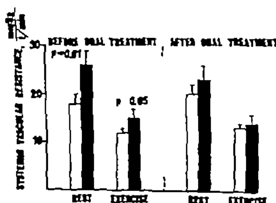
Figure 2 shows the results for strok olume. Propranolol injection caused no significant changes either before or after the long-term oral therapy However the spontaneous stroke olume during exercise was *significantly* increased *after* long-term treatment in way similar to that seen after a period of intense physical training which is in agreement with the results found by Pernow et al *presented here today*



Lundman Fig. 1



Lundman Fig 2



Lundman Fig 3

Figure 3 shows the results for systemic ascular resistance. Before long-term treatment the systemic vascular resistance was significantly increased both at rest and during exercise. After long-term treatment no significant effects were obtained by propranolol injection.

To conclude the study shows that haemodyna-

sympathetic neurotransmitter noradrenaline. Maximal tension was slightly higher in strips from hypertensive patients, but the difference was not statistically significant ($p<0.10$)

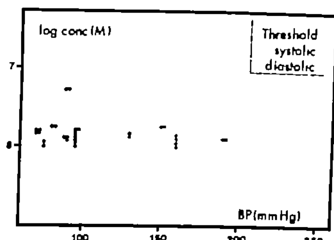


Fig 1 Threshold towards noradrenaline (M = molar) in relation to systolic and diastolic blood pressure

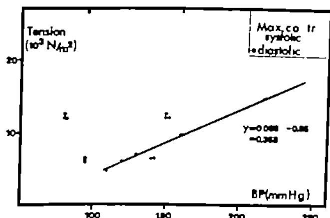


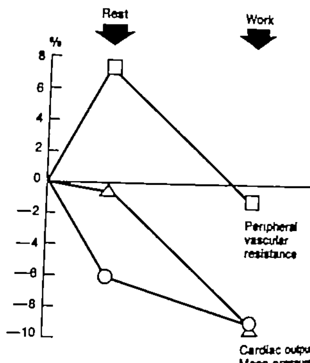
Fig 2. Maximal force to contraction given as tension (N = Newton) per cross-sectional area (m^2) in relation to systolic and diastolic blood pressure. Regression equation correlates systolic pressure and tension

Per Bjerle

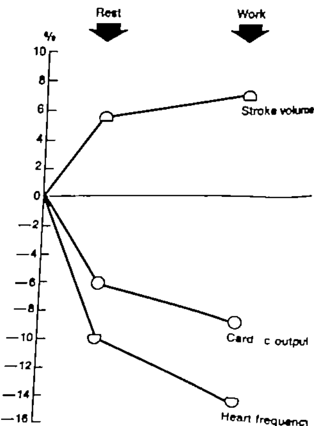
In many studies it has been shown that the antihypertensive effect of beta blockers develops gradually

Initially most beta-blockers raise peripheral vascular resistance, but then during continued therapy the resistance gradually returns to the initial value

Professor Pernow has now reported a statistically significant decrease of peripheral vascular resistance after 8 weeks of pindolol treatment. But what happens initially? To answer that question the following study carried out at the departments of Cardiology and Clinical Physiology at the university of Umeå may be of interest although it



Bjerle Fig. 1



Bjerle Fig. 2

Clinical Pharmacology of Beta Adrenoceptor Blocking Agents

Chairman Nils Svedmyr

Clinical Pharmacology Laboratory Lung Clinic Renströmska Hospital Göteborg Sweden

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Ramon Sivertsson
Pernow s paper showing that pindolol reduces re sistance, was very interesting. With this pindolol effect in mind, I would like to comment further on the results, which I showed you before. After 6 months treatment with atenolol we observed a considerable rise in resistance. Treatment with mefruside the saluretic drug, did not change the resistance. My question to the audience is now What conclusions can be drawn from these hae modynamic findings regarding the practical use of these drugs? Should we prefer one drug rather than another and if so which drug?

One more comment, and this is to Pernow's discussion It is a very interesting thought that structural changes may be responsible for the change in the haemodynamic picture between 2 and 16 months But I do not think, that the re sults presented can prove such a change. The fore-arm resistance values did not refer to maximal dilatation, as far as I understood, but rather to a resting situation in the arm. If so changes in smooth muscle tone can explain the results as well.

Per Lund Johansen
Just a short comment on the question about the possibility of reversing structural changes. In one of the last issues of "Circulation there is a very interesting paper on patients who have been oper ated on for coarction in the aorta and been re studied ten years later The blood flow and the re sistance to flow were measured in the arms and in the legs. In spite of the fact that the operation was successful, pathological changes in blood flow and resistance in the arms were still demonstrable. In the legs and the vascular areas which had been pro-tected from the high blood pressure blood flow and resistance were still normal.

Göran Berglund
I have a question for Ramon Sivertsson as well. Did you find any correlation between the blood pres-sure decrease and the decrease in resistance at maximal dilatation? In other words, is a good blood pressure decrease characterising those pa tients who respond with a decrease in resistance at maximal dilatation?

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The last study I mentioned is not finished but as far as I can remember there is a correlation be tween change in pressure and change in resistance at rest

Olav Thulesius
I have a question for Bengt Pernow I think it is very important to look at changes in venous tone and these have not been studied as much as they should be, but I think that such a study involves a very difficult technique. I noticed that you had an increase in venous pressure but no increase in volume. You measured changes during an increase in both volume and pressure, but you do not know the basal blood volume in the vessels. In order to compare sets of measurements, it is essential to know the initial volume in the vessel, and that is very hard to determine.

Bengt Pernow
I agree with Thulesius, that this is a very tricky technique and perhaps that is why so few studies have been performed on the compliance vessel si-tuation of patients. As I showed, this technique by Sharpey Schafer records the increase in volume and the increase in pressure simultaneously and from this ratio one can get a rough idea of the ve nous tone. There are other methods, which we have also used. One can get a pressure volume curve by increasing the venous pressure of the forearm sett ing the pressure at different levels. One gets almost the same results with this technique.

Kjell Haglund
It is often stated that beta-adrenergic blocking drugs have no acute antihypertensive effects. We have found with metoprolol, which is a cardio-selective beta-blocking agent and probably also with alprenolol that after peroral medication the blood pressure decreased significantly within one hour and was still significantly decreased eight hours after administration. We do not think, that you will have to wait a fortnight or more to get the antihypertensive effect.

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However it is striking how well the haemody-namic pattern with successive reduction of cardiac output and increase of peripheral resistance during the development of hypertension as described by Per Lund Johansen fits with the concept derived from the results of Ramon Sivertsson s study on the appearance of structural changes in the resist ance vessels. His conclusion that these structural vascular changes might be partially reversible dur ing long-term blood pressure lowering therapy is in agreement with the results which Bengt Pernow reported today

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Pindolol A Pharmacokinetic Comparison with other Beta Adrenoceptor Blocking Agents

Jürg Meier

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Basle Switzerland

Abstract. The pharmacokinetic properties of the nine most frequently studied β-adrenoceptor blocking agents (alprenolol, atenolol, metoprolol, oxprenolol, pindolol, practolol, propranolol, sotalol and timolol) were compared. Some pharmacokinetic parameters were found to be quite similar or at least not relevantly different in this group of drugs: e.g. the rate and the amount of absorption, the distribution volume, the elimination half-life, the total clearance and the total urinary excretion. However some other pharmacokinetic parameters: e.g. the daily dosage, the oral bioavailability the first-pass effect and the ratio of renal versus hepatic clearance, were surprisingly different in this series of drugs. A good correlation between systemic availability and urinary excretion of unchanged drug could be demonstrated for the beta-adrenoceptor blocking agents.

The pharmacokinetic comparison in this series of beta-blockers revealed that pindolol has some relevant advantages. Due to the moderate metabolism, negligibl first-pass effect results which yields a high oral bioavailability and leads to small interindividual variations in plasma levels and effects. As a result of the balanced clearance by the liver and the kidney and probably some compensating factors, no accumulation of pindolol has to be expected in patients with partial liver or kidney impairment. Therefore, apart from possessing the lowest daily dosage of the studied beta-blockers, pindolol administration is relatively less likely to be critical in patients with partial renal or hepatic insufficiency

The clinical pharmacokinetics of most β-adrenoceptor blocking drugs have been well studied in the last few years. The most recent and comprehensive review has been published by Johnsson and Regårdh (12). In this paper the nine most frequently studied beta-adrenoceptor blocking drugs are compared in respect to their pharmacokinetic similarities and differences. Some newer data of pindolol from various authors will be included and the clinical significance of the observed pharmacokinetic differences will be discussed

SIMILARITIES AND DIFFERENCES

In view of the chemical structures of the beta-adrenoceptor blocking drugs, both similarities and differences can be expected in the pharmacokinetic parameters. The isopropylaminopropoxy side chain is common to seven of the nine β-blockers listed in Table 1 Sotalol and timolol have slightly different side chains. The bulk of the molecules consists of an aromatic ring system, however which is different for each beta-adrenoceptor blocking agent (12)

The pharmacokinetic parameters of β-blockers which are similar or at least not in a clinically significant way different, are summarized in Table 1 All the beta-adrenoceptor blocking agents compared have a fast and complete absorption. One possible exception is atenolol (9 14) for which a slower and apparently less complete absorption is reported. In all cases the distribution volumes exceed by far the available body space. Therefore the beta-adrenoceptor blocking agents are well distributed into the tissues. The plasma protein binding is generally low for the beta-blockers. The protein binding is highest for propranolol (93%), and alprenolol (85%) but even in these cases the plasma protein binding is not critical in view of the large distribution volume. No drug interactions based on a displacement mechanism are known or to be expected.

Table 2. Pharmacokinetic parameters of ß-blockers which are different.

ß-blocker	Daily dose mg	Bioavailability oral, %	Dose dependent bioavailability	Urinary excretion unchanged drug, %	First-pass effect %	Accumulation expected	
						Liver disease	Renal failure
Alprenolol	400	≈10	Yes	<1	≈90	—	—
Atenolol	200	≥40	No	≈40	<15	—	—
Metoprolol	300	≈50	No	≈3	≈50	—	—
Oxprenolol	160	24—60	No	2—5	30—50	—	—
Pindolol	15	87	No	≈40	13	No	No
Practolol	400	100	No	>90	0	No	Yes
Propranolol	300	30	Yes	<1	≈60	Yes	Yes
Sotalol	240	≥60	Not likely	≈60	≤15	—	Yes
Timolol	30	—	Not likely	≈20	—	—	—

[Partly from Johnsson and Regårdh, Clinical pharmacokinetics 1 233 1976]

the first-pass effect. The disadvantage of a strong first-pass effect is not only the lower availability after oral administration, which can be compensated by a higher dosage, but also the resulting larger biological, individual variation in the plasma levels and drug response (2,22). For alprenolol and propranolol the bearing of the first-pass effect on the pharmacokinetics is accentuated by the resulting non-linear oral bioavailability. On the other hand, the formation of pharmacologically active metabolites, as reported by Ablad et al. (1) Bodin et al. (5) and Paterson et al. (20) for these two drugs, can partly compensate the disadvantages of the strong first-pass effect. However the active metabolite 4-hydroxy-propranolol contributes only with a smaller and even faster eliminating plasma level (20) than the parent drug itself.

For pindolol a negligible first-pass effect is reported in man (15). An investigation of the absorption and the first-pass effect of pindolol in the dog (16) revealed that the low first-pass effect observed with pindolol in man is not a property of the molecule as such, but rather correlates with the extent of metabolism. This is demonstrated in Figure 1 where the systemic availabilities of a few beta-adrenoceptor blocking agents are plotted against their urinary excretion on a logarithmic scale. This representation is of course analogous to a graph in which the magnitude of the first-pass effect is plotted against the extent of metabolism. According to Figure 1 practolol is not metabolised and has a very good systemic availability. In man pindolol is eliminated to about 40% as unchanged drug in the urine and has an almost complete oral bioavailability (87%) with a negligible first-pass effect (15). Next in the row is pindolol in the dog with a rather strong hepatic degradation and a medium first-pass effect (16). Then metropolol, oxprenolol, propranolol and finally alprenolol, which is almost completely metabolised and has a very strong first-pass effect, are following in Figure 1. As expected from the different first-pass effects of beta-blockers, the individual variations are large for e.g. alprenolol (2,22) and propranolol (8) and small for e.g. pindolol after both single and multiple oral administration (10). Since there is a definite correlation between plasma levels and effects (21) these differences are of clinical relevance, even though the plasma level response curve seems rather flat (21).

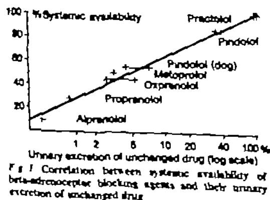


Fig. 1 Correlation between systemic availability of beta-adrenoceptor blocking agents and their urinary excretion of unchanged drug

Table 1 Pharmacokinetic parameters of ß-blockers which are similar

ß-blocker	Absorption T_{max} (H)	% of dose	Distribution volume l/kg	Protein binding (human serum) %	Elimination half-life (H)	Total clearance (l/Min)	Total urina excretion ('
Alprenolol	0.5—1.5	90	3.3	85	2—3	1.2	>90
Atenolol	2—4	>50	—	—	6—9	—	—
Metoprolol	0.5—1.5	>95	5 6	12	3—4	1 1	>95
Oxprenolol	0.5—1	70—95	1.2	—	1—2	0 6	70—95
Pindolol	1.5—2	>95	2.0	40	3—4	0.4	>90
Practolol	1—3	>95	1 6	—	5—13	0.14	>90
Propranolol	1—3	>90	3 6	93	2—3	1 0	>90
Sotalol	2—3	>75	—	—	5—6	—	—
Timolol	1—3	>90	—	—	4—5	—	73

[Partly from Johnsson and Regårdh, Clinical pharmacokinetics, 1, 233 1976]

In general the elimination half lives of the beta blockers are short and range between 1—2 hours for oxprenolol up to 5—13 hours for practolol Most beta-blockers are therefore dosed three times daily *However twice or once daily application is* possible for beta-blockers, because the effects do not decline linearly with the plasma levels *but with* a slower zero-order kinetics (13) The response of beta blockers is therefore longer than we might expect from the relatively short elimination half lives. The clearance of practolol is lowest due to the slowest elimination constant. The beta-blockers and/or their metabolites are mainly cleared via the kidney (*70—100% of the absorbed dose*). This column in Table 1 refers to the total urinary excretion of radioactively labelled drug substance which includes the parent drug and its metabolites.

Table 2 summarizes the pharmacokinetic parameters of betaadrenoceptor blocking drugs which *are different and have a clinical relevance in their difference The daily dosage varies greatly from* pindolol (about 15 mg per day) to alprenolol and practolol (about 400 mg per day) Based on "ecological" considerations (clearance, saturation of enzyme and eliminationsystems, drug interactions and competitive bindings) a small amount of a potent drug is advantageous for a patient especially *in chronic treatment and* when many other drugs have to be administered *simultaneously* Large differences can further be observed in the oral *bioavailabilities* which are highest for practolol and pindolol (100 and 87%) and lowest for alprenolol and propranolol (10 and 30%). There i no direct correlation between bioavailability an necessary daily dosage because the two highe dosed beta-blockers, alprenolol and practolol, ha *the lowest and highest bioavailability In two case* alprenolol and propranolol the strong first-pass ef*fect which is responsible for the low oral bioavail*ability is not dose linear due to the saturation o drug extraction by the liver (12). Great difference are also observed in the column "urinary excretio of unchanged drug" Practolol is practically no metabolised but excreted as unchanged drug by the kidneys. On the other hand alprenolol me*toprolol oxprenolol and propranolol* are very intensively metabolised and very little unchanged drug is excreted in the urine. Atenolol pindolol, sotalol and timolol are cleared to various degree *by the kidneys and by the liver The main differ*ences in the pharmacokinetics of beta-adrenoceptor blocking agents are therefore "the first-pass effect" and "the clearance These topics will be elaborated in the following paragraphs

FIRST PASS EFFECT

Great variations in the oral bioavailabilities of the nine beta-adrenoceptor blocking agents *are listed in Table 2, even though the absorption has been* shown to be fast and complete in Table 1 The major cause of the low bioavailability of most beta-adrenoceptor blocking agents is a high first pass effect. *Metabolism by the liver during its* first passage after oral absorption is referred to as

Table 3 Pharmacokinetically based advantages of Pindolol in therapy

PHARMACOKINETIC FACTS	THERAPEUTICAL ADVANTAGES
— High bioavailability	— Low daily dosage
— Low first-pass effect	— No saturation effects
— Moderate metabolism	— Small variations in plasma levels and effects
— Low protein binding	
— Balanced clearance by the kidney and the liver	— No accumulation of Pindolol in patients with renal or hepatic impairment (not critical in dosing)
— Partly compensating factors in liver or kidney insufficiency	

low first-pass effect and the low dosage small variations in plasma levels and effects due to the low first-pass effect, the moderate metabolism and the low protein binding; and finally no accumulation of pindolol has to be expected in patients with renal or hepatic impairment due to the balanced clearance and probably some compensating factors

REFERENCES

1 Ablad, B Borg, K. O Johnsson, G., Regårdh, C.-G & Sölvell, L. Combined pharmacokinetic and pharmacodynamic studies on alprenolol and 4-hydroxy-alprenolol in man. Life Sciences 14 693 1974.

2 on Bahr C Alvan, G Lind, M Mellström, B. & Sjöqvist, F First-pass effect and dose dependent availability as factors contributing to inter individual differences in equilibrium concentrations of alprenolol in man. Acta pharm. Suecica 11 649 1974

3 Baber L R. I Kaye C M & Kumana, C R Influence of renal function on practolol elimination Br J clin Pharmacol 10, (2) 136, 1974

4 Bianchetti, G Graziani, G Brancaccio D Morganti, A Leonetti, G Mandina, M Sega, R Conrad R Pontrelli, C & Morselli, P L Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment Clinical Pharmacokinetics 1 373 1976

5 Bodin, N-O Borg K O Johansson, R., Obianwu, H & Svensson, R Absorption, distribution and excretion of alprenolol in man, dog and rat. Acta pharmacol et toxicol 35 261 1974

6 Bodem, G Gruner H Eichelbaum, M & Gugler R. Pharmacokinetics of practolol in renal failure Europ J clin Pharmacol. 7 249 1974

7 Branch, R A James, J & Read, A. E. The pharmacokinetics of (+)-propranolol in normal subjects and patients with chronic liver disease. Brit. J clin. Pharmacol. 2: 183 P 1975

8. Chidsey C. A., Morselli, P Bianchetti, G., Morganti, A., Leonetti, G. & Zanchetti, A.. Studies of the absorption and removal of propranolol in hypertensive patients during therapy Circulation 52, 313 1975

9 Graham, B. R., Littlejohns, D W Prichard, B. N C. Scales, B & Southorn, P Preliminary observation on the human pharmacology of I.C.I. 66082 in normal volunteers. Brit. J Pharmacol. 49 154 P 1973

10 Gugler R Bodem, G. & Dengler H. J Plasmaspiegel von Pindolol (Visken®) unter Dauerbehandlung, berechnet aus der Pharmakokinetik nach Einzeldosis. Verhandlungen der deutschen Gesellschaft für innere Medizin, in press, 1976

11 Lavene, D Weiss, Y A., Safar M. E., Loria, Y., Georges, D & Milliez, P L. Pharmacokinetics and hepatic extraction ratio of pindolol in hypertensive patients with normal and impaired renal function. J clin. Pharmacol., in press, 1977

12 Johnsson, G. & Regårdh, C.-G Clinical pharmacokinetics of β-adrenoreceptor blocking drugs. Clinical Pharmacokinetics 1 233, 1976.

13 Johnsson, G. & Regårdh C.-G Clinical Pharmacokinetics of β-adrenoreceptor blockers. Drugs 11 (Suppl. 1). 111 1976.

14 Marlin, G. P Kumana, C. R., Kaye C. M. Smith, D M & Turner P An investigation into the cardiac and pulmonary β-adrenoceptor blocking activity of I.C.I. 66082 in man. Br J clin. Pharmac. 2. 151 1975

15 Meier J & Nüesch, E. Pindolol, beta-adrenoceptor blocking agent with negligible first-pass effect Br J clin. Pharmac in press, 1977

16. Meier J & Wagner O First-pass effect of the beta-adrenoceptor blocking agent pindolol in the dog. Brit. J Pharmacol., in press, 1977

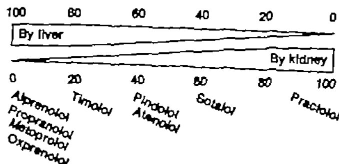


Fig 2 Clearance of beta-adrenoceptor blocking agents by the liver and/or the kidney

CLEARANCE

Figure 2 demonstrates the clearance of the nine beta-adrenoceptor blocking agents by the kidney and/or the liver There is a large difference in the way of clearance. Practolol is almost completely cleared by the kidneys. In kidney insufficiency therefore the dosage has to be reduced due to the smaller elimination kinetics (6 3). On the other hand the beta-blockers alprenolol propranolol *metoprolol and oxprenolol are almost completely* eliminated by hepatic metabolism. For propranolol Branch et al. (7) could *show that the clearance* decreased with the evidence of increasing severity in liver function impairment. Pindolol and probably also timolol atenolol and sotalol are cleared partly by the kidneys and partly by the liver On theoretical grounds, an impairment of the liver or kidney function cannot be so critical For pindolol *it could be shown experimentally that the dosage* regimen is not critical in patients with renal or *hepatic impairment and that probably even a cer*tain degree of compensating clearance occurs if the function of the liver or the kidney is reduced. Ohnhaus et al (17) determined the elimination constants of pindolol in patients with varying degrees of kidney impairment. The elimination constants varied between 0 1 and 0.3 hours $^{-1}$ without significantly decreasing even at *very low or zero* creatinine clearance Øie and Levy (19) found a *positive correlation* between the renal clearance of pindolol and the creatinine clearance, but no statistically significant correlation (n=24 patients) was observed between the important over all clearance of pindolol and the creatinine clearance. In a very recent investigation *(11) pindolol* showed a decreased clearance in hypertensive patients with impaired renal function after intravenous and oral administration. However *due to a reduced* absorption after oral administration, the plasma levels in the group with impaired renal function were only slightly higher (maximal plasma levels 40 instead of 30 ng/ml after single dose or simulated multiple dosing) compared to the patients with normal renal function. Therefore, no relevant accumulation of pindolol seems to occur in patients with renal impairment, whereas for propranolol *Bianchetti et al. (4)* report a 7 to *10-fold* increase of plasma concentrations in uraemic patients. *Propranolol should be used with great cau*tion and at low doses in chronic renal failure according to these authors (4) For sotalol the mean plasma half-life was prolonged from 5 hours (normals) to 42 hours in patients with renal failure (23) Little is published about the pharmacokinetics of betablockers in liver disease For propranolol (12) the drug clearance decreased in liver disease to 0.29 L/min (normal 1 0 L/min) and the plasma half-life increased to 18 hours (normal 2 to 3 hours). Due to the smaller extent of hepatic ex*traction the total clearance of pindolol* seems to be less affected in patients with liver disease. No correlation has been found between antipyrine clearance (parameter of the metabolic capacity of the liver microsomal enzyme system) and the total body clearance of pindolol since some patients with intact renal function excreted a higher portion of pindolol in the urine as *liver function de*creased (18) Only in cases with real liver failure *(antipyrine clearances less than 10 ml/min)* did the clearance of pindolol decrease (18), and the dosage would have to be adjusted.

CONCLUSIONS

There are a number of similarities in the pharmacokinetic properties of the current beta-adrenoceptor blocking agents (Table 1). There are also some different pharmacokinetic parameters (Table 2), some of which are of clinical relevance. Especially for pindolol (Table 3) quite a series of interesting and valuable pharmacokinetic parameters can be summarized (left side of Table 3). The resulting therapeutical advantages are the following: *a low daily dosage based on the high bio*availability the low first pass effect, the moderate metabolism and mainly of course due to the potency of the drug: no saturation effects due to the

Investigations with Beta Adrenoceptor Blocking Drugs in Healthy Volunteers

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Abstract. Several properties of beta-adrenoceptor blocking drugs can be investigated in healthy volunteers with simple non-invasive techniques giving reproducible results.

Beta-adrenoceptor blocking activity can be evaluated in several ways. One is to compare heart rate during physical exercise before and after drug administration. 5 mg pindolol and 100 mg propranolol were about equiactive in this test.

Another method is to administer i.v. infusions of isoprenaline before and after the administration of the antagonist and to determine the dose of isoprenaline required to increase heart rate to 120 beats/min. Pindolol is about 40 times more potent than propranolol and Sandoz 23-784 about 10 times more potent than pindolol in this test.

The moderate intrinsic sympathomimetic activity (ISA) of pindolol leads to a slight increase in resting heart rate of subjects in the supine position when sympathetic tone is very low. In the sitting position pindolol like propranolol (without ISA) reduces resting heart rate (but to a lesser extent). Sandoz 23-784, a drug with high ISA, increases resting heart rate both in the supine and in the sitting position. For comparative studies on the duration of action of different drugs exercise-induced tachycardia seems most convenient. Experiments have shown that in equipotent doses pindolol (5 mg) exhibits a longer duration of action than propranolol (100 mg).

Studies on the beta-adrenoceptor blocking activity of pindolol after oral and after i.v. administration support the results of pharmacokinetic studies showing nearly complete absorption and a small first pass effect for this drug in man.

*) This paper is a synthesis of lectures given at this symposium and at the symposium Betablockade Hypertension Basle 27/28 January 1977

INTRODUCTION

The aim of the present symposium is to discuss various aspects of hypertension and especially its treatment. The beneficial effect of beta-adrenoceptor blocking drugs in the treatment of hypertension is well established. Many different beta-adrenoceptor blocking drugs are available today and all are effective in the treatment of hypertension, and, of course, also angina pectoris. The therapeutic effectiveness in these indications is attributed to their clearly defined pharmacological action and not to a nonspecific effect, such as local anaesthetic activity (9 10 11).

The spectrum of pharmacological properties of these various drugs is not identical. In addition to their common property of blocking beta-adrenoceptors, some compounds possess e.g. intrinsic sympathomimetic activity. The duration of action of the different substances is not the same and also the bioavailability varies from drug to drug. In my contribution to this symposium I would like to discuss how several properties of beta-adrenoceptor blocking drugs can be investigated in healthy volunteers with simple non-invasive and reproducible techniques. Most of the examples shown are taken from studies with pindolol and propranolol (1 2, 3 4).

ACTIVITY

Beta-adrenoceptor blockade can be evaluated in healthy volunteers in several different ways. One is to compare heart rate and systolic blood pressure during physical exercise before and after drug administration. An example of an experiment with pindolol (5 mg p.o.) (5) is shown in Figure 1. Five healthy volunteers exercised on a bicycle ergometer with a work load of 150 Watts for 3 min. This produced a mean increase in heart

17 Ohnhaus E. E. Nüesch E., Meier J & Kalberer F.. *Pharmacokinetics of unlabelled and 14C-labelled pindolol in uraemia* Europ J clin Pharmacol. 7 25 1974

18 Ohnhaus E. E Münch U & Meier J Vergleichende Untersuchung zur Elimination von *Pindolol* (Visken) und Antipyrin bei Patienten mit Lebererkrankungen. Schweiz. med Wschr 106 Nr 49· 1748 1976.

19 Øie S. & Levy G.. Relationship between renal function and elimination kinetics of pindolol in *man. Europ J clin Pharmacol. 9 115 1975*

20 Paterson J W Conolly M E Dollery C. T *Hayes A. & Cooper R. G The pharmacodyna*mics and metabolism of propranolol in man. Pharmacologia Clinica 2. 127 1970

21 Pine M Favrot L Smith S McDonald K & Chidsey C. A Correlation of plasma propranolol *concentration with therapeutic response in pa*tients with angina pectoris Circulation 52. 886 1975

22. Rawlins, M D Collste P Frisk Holmberg M Lind M Östman J & Sjöqvist F.. Steady-state *plasma concentrations of alprenolol in man* Europ J clin. Pharmacol. 7 353 1974

23 Tjandramaga T B Thomas J Verbeeck R., Verbesselt, R. Verbereckmoes, R & de Schepper P J The effect of the end-stage renal failure and haemodialysis on the elimination kinetics of sotalol. Br J clin Pharmac 3 259 1976.

DISCUSSION

Lennart Hansson
I would like to say a few words to Dr Meier I think that you perhaps overstate the importance of a high first pass effect. Your criticism is valid only if the metabolites are not active. But in the case for example of alprenolol and propranolol we know that the metabolites are also active For the clinician it is the degree of beta blockade that is of interest and he does not care whether that is obtained with the initial drug or with its metabolites.

Bengt Pernow
Are there any data on the passage of these drugs through the blood brain barrier?

Pavel Jerie
Pindolol passes into the brain after 10 to 12 minutes and this can be shown by its effect on the EEG

Hans Åberg
Neither atenolol nor metoprolol seem to penetrate the blood brain barrier

Kjell Haglund
I do not agree with Hans Åberg. We know that metoprolol and probably atenolol enter the cerebrospinal fluid but the effect of the drugs with the central nervous system is unclear

Nils Svedmyr
I think that all beta blockers enter the blood-brai barrier

Investigations with Beta Adrenoceptor Blocking Drugs in Healthy Volunteers

Walter H. Aellig

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Abstract. Several properties of beta-adrenoceptor blocking drugs can be investigated in healthy volunteers with simple non-invasive techniques giving reproducible results.

Beta-adrenoceptor blocking activity can be evaluated in several ways. One is to compare heart rate during physical exercise before and after drug administration. 5 mg pindolol and 100 mg propranolol were about equiactive in this test.

Another method is to administer i.v. infusions of isoprenaline before and after the administration of the antagonist and to determine the dose of isoprenaline required to increase heart rate to 120 beats/min. Pindolol is about 40 times more potent than propranolol and Sandoz 23-784 about 10 times more potent than pindolol in this test.

The moderate intrinsic sympathomimetic activity (ISA) of pindolol leads to a slight increase in resting heart rate of subjects in the supine position when sympathetic tone is very low. In the sitting position pindolol like propranolol (without ISA) reduces resting heart rate (but to a lesser extent). Sandoz 23-784, a drug with high ISA, increases resting heart rate both in the supine and in the sitting position. For comparative studies on the duration of action of different drugs exercise-induced tachycardia seems most convenient. Experiments have shown that in equipotent doses pindolol (5 mg) exhibits a longer duration of action than propranolol (100 mg).

Studies on the beta-adrenoceptor blocking activity of pindolol after oral and after i.v. administration support the results of pharmacokinetic studies showing a nearly complete absorption and small first pass effect for this drug in man.

**) This paper is a synthesis of lectures given at this symposium and at the symposium "Betablockade in Hypertension", Basle 27/28 January 1977*

INTRODUCTION

The aim of the present symposium is to discuss various aspects of hypertension and especially its treatment. The beneficial effect of beta-adrenoceptor blocking drugs in the treatment of hypertension is well established. Many different beta-adrenoceptor blocking drugs are available today and all are effective in the treatment of hypertension, and, of course, also angina pectoris. The therapeutic effectiveness in these indications is attributed to their clearly defined pharmacological action and not to a nonspecific effect, such as local anaesthetic activity (9, 10, 11).

The spectrum of pharmacological properties of these various drugs is not identical. In addition to their common property of blocking beta-adrenoceptors, some compounds possess e.g. intrinsic sympathomimetic activity. The duration of action of the different substances is not the same and also the bioavailability varies from drug to drug. In my contribution to this symposium I would like to discuss how several properties of beta-adrenoceptor blocking drugs can be investigated in healthy volunteers with simple non-invasive and reproducible techniques. Most of the examples shown are taken from studies with pindolol and propranolol (1, 2, 3, 4).

ACTIVITY

Beta-adrenoceptor blockade can be evaluated in healthy volunteers in several different ways. One is to compare heart rate and systolic blood pressure during physical exercise before and after drug administration. An example of an experiment with pindolol (5 mg p.o.) (3) is shown in Figure 1. Five healthy volunteers exercised on a bicycle ergometer with a work load of 150 Watts for 3 min. This produced a mean increase in heart

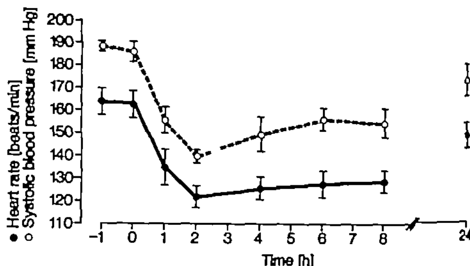


Fig 1 Heart rate and systolic blood pressure at the end of 3 min exercise (150 Watt) on the bicycle ergometer before and after oral administration of 5 mg pindolol (mean±s.e. n=5 data from Aellig, 1976 [3])

rate from 96±6 (mean±s.e.) to 163±6 beats/min. Systolic blood pressure was increased from 121±3 mm Hg to 186±5 mm Hg.

The figure shows that heart rate at the end of exercise was markedly reduced within one hour after oral administration of pindolol and reached its minimum with 122±5 beats/min after 2 hours. Systolic blood pressure at the end of exercise was reduced in a similar way to a value of 140±3 mm Hg after 2 hours. If we carry out the same experiment with different drugs, the maximum reduction in exercise induced tachycardia is a measure of the relative activity of the different doses of the drugs investigated. In the example shown in the figure we also studied the effect of propranolol and it was found that the maximum reduction of exercise induced tachycardia was also observed 2 hours after oral administration. The effect of 100 mg propranolol was with 41 beats/min comparable to that seen after 5 mg pindolol (42 beats/min) As higher doses of both drugs produced a greater reduction in exercise induced tachycardia, it was concluded that the effects seen after the doses used of both drugs were still on the ascending part of the dose-response curve and that therefore 5 mg of pindolol and 100 mg propranolol were about equiactive in this test.

Another way to assess comparative beta-adrenoceptor blocking activity is to administer intravenous infusions of the beta-adrenoceptor stimulant drug isoprenaline before and after administration of a beta-adrenoceptor blocking drug and to determine the dose of isoprenaline which is required to produce a given increase in heart rate or a given heart rate value. Although intravenous infusions of isoprenaline are easy to administer and produce reproducible results, exercise-induced tachycardia seems to be more closely related to the physiological beta adrenoceptor stimulation occurring in normal life.

In our experiments isoprenaline hydrochloride was infused into a left forearm vein of the subject resting in the supine position. The starting dose was 2 μg/min and was doubled every 5 minutes until a heart rate of at least 120 beats/min was reached. A higher starting dose was used after the administration of the beta-adrenoceptor blocking drugs.

Increasing doses of the beta adrenoceptor blocking drugs lead to a dose-dependent parallel shift of the isoprenaline dose-response curves to the right. This is typical for a competitive antagonism. For any dose of a beta-adrenoceptor blocking drug a dose of isoprenaline can be found which will produce a given increase in heart rate there exists no "complete beta-blockade" From these curves the dose of isoprenaline required to increase heart rate to 120 beats/min was determined for every subject after each dose of the different drugs.

Figure 2 shows the results of a comparative study with pindolol and propranolol (3) and of a recent investigation with Sandoz 23-784 (4-(3-tert. Butylamino-2-pivaloyloxypropoxy)-2 indolinone hydrochloride). It is evident that all three beta adrenoceptor blocking drugs lead to a dose-dependent increase of the dose of isoprenaline re-

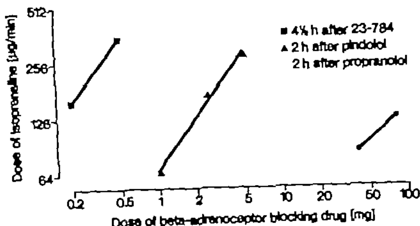


Fig. 2. Dose of isoprenaline required for a heart rate of 120 beats/min after oral administration of various doses of pindolol (n=3), propranolol (n=3), and 23-784 (n=4) (data for pindolol and propranolol from Aellig, 1976 [3]).

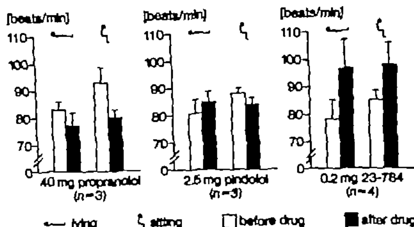


Fig. 3. Resting heart rate in the lying and in the sitting position before and two hours after oral administration of 2.5 mg pindolol and 40 mg propranolol and before and 4½ hours after oral administration of 0.2 mg 23-784 (mean ± s.e., data for pindolol and propranolol from Aellig, 1976, [3,5]).

quired to achieve a heart rate of 120 beats/min. The times chosen for the determination of the isoprenaline dose (i.e. 2 hours after pindolol and propranolol and 4½ hours after 23-784) were those at which maximum effect was seen. The dose-response curves in Figure 2 are practically parallel and an evaluation of the distances between them shows that pindolol is about 40 times more potent than propranolol (1, 3) and 23-784 is about 10 times more potent than pindolol in this experimental model. From these results it would seem that 23-784 was a highly active beta-adrenoceptor blocking drug, potentially useful in the therapeutic indication of these drugs. The results presented in the next section, however, will show otherwise.

INTRINSIC SYMPATHOMIMETIC ACTIVITY (ISA)

Some beta-adrenoceptor blocking drugs themselves stimulate beta-adrenoceptors. This property is called intrinsic sympathomimetic activity (ISA). Figure 3 shows that the ISA of a drug like pindolol leads to a slight increase in resting heart rate of subjects in the supine position where sympathetic tone is very low. In the sitting position, when sympathetic tone is higher, pindolol like propranolol (a drug without ISA) reduces heart rate, but to a lesser extent (3). If we now look at the results with 23-784, we see that this drug increases resting heart rate not only in the lying position (and to a greater extent than pindolol) but also in the sitting subject. The mean heart rate

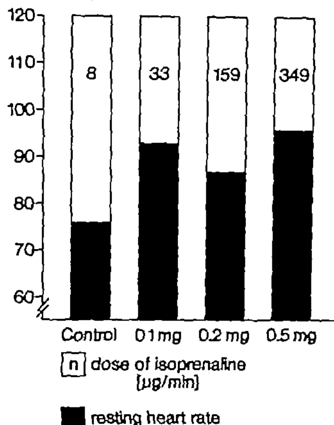


Fig 4 Resting heart rate in the lying position and dose of isoprenaline required for a heart rate of 120 beats/min before and 4½ hours after oral administration of 23—784 (mean n=3) The increase in resting heart rate shown on this figure is smaller than that seen in figure 3 the reason being that isoprenaline infusions could only be administered to 3 of the 4 subjects of figure 3 as in the fourth one heart rate had already reached a value above 120 beats/min without isoprenaline.

values reached after 4½ hours were 97±10 beats/min in the lying and 98±8 beats/min in the sitting position, compared with pre-drug values of 78±7 beats/min and 85±4 beats/min respectively Figure 4 gives a synopsis of the effects of 23-784 on resting heart rate in the lying position and of the dose of isoprenaline required to increase heart rate to 120 beats/min The figure demonstrates again the high beta-adrenoceptor blocking activity of 23-784 due to the higher resting values the large doses of isoprenaline required after oral administration of the drug were actually producing a much smaller rise in heart rate than in the control period It may be concluded that pindolol possesses what might be called a well balanced ISA which seems to be an advantage in so far as the drug neither leads to a great reduction nor to a great increase in resting heart rate. In contrast 23-784 despite its high beta-adrenoceptor blocking potency exerts too much intrinsic sympathomimetic activity to be of use in the traditional indications of beta-adrenoceptor blocking drugs.

DURATION OF ACTION

Exercise-induced tachycardia is not only useful for investigating the potency but also the duration of action of a beta-adrenoceptor blocking drug. If equipotent submaximal doses of different drugs are administered, the experiment allows a comparison of the duration of action of these drugs.

Our experiments with pindolol (5 mg) and propranolol (100 mg) showed that the doses used of both drugs are about equiactive 2 hours after oral administration. The duration of action of pindolol however is clearly longer than that of propranolol Whereas after 24 hours 16±4% of the effect of propranolol remained, at this time pindolol showed 36±5% of the maximum (2, 3).

The long duration of action of pindolol has been confirmed in several therapeutic studies in patients with essential hypertension where the drug was administered once or twice daily (6, 12).

BIOAVAILABILITY

The pharmacokinetics of beta-adrenoceptor blocking drugs have been reviewed by J Meier (8) in the same issue of this journal His paper shows that after oral administration of beta-adrenoceptor blocking drugs the amount of drug absorbed and also the amount of drug metabolized during the first passage through the liver (first pass effect) varies for the different substances. In order to know how much of the orally administered drug is available at the receptor site it seems therefore important to compare the effects of these drugs after oral and after intravenous administration.

In a study with oral and intravenous administration of different doses of pindolol beta-adrenoceptor blocking activity was determined on isoprenaline and exercise-induced tachycardia (4)

The results show that the activity found hours after oral administration is about the same as that seen 75 min after intravenous administration of the same dose. These results therefore support those of the pharmacokinetic studies showing a nearly complete absorption of pindolol (7 8) and a small first pass effect in man (8)

REFERENCES
1 Aellig, W. H. Isoprenaline antagonism and duration of action in exercise-induced tachycardia of three beta-adrenoceptor blocking drugs: pindolol, LF 17-895 and propranolol. Brit. J. Pharmac. 47 621P 1973
2. Aellig, W. H. and Saameli, K., Prolonged action of pindolol. Brit. med. J. 2: 365 1973
3. Aellig, W. H. Beta-adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. Br. J. clin. Pharmac. 3 251 1976.
4. Aellig, W. H.. Klinisch-pharmakologische Untersuchungen mit Pindolol nach intravenöser und oraler Verabreichung. Advances Clin. Pharmacol. 11 9 1976
5. Aellig, W. H. Clinical pharmacological experiments with two beta-adrenoceptor blocking drugs, pindolol and propranolol. In. Beta-adrenoceptor blocking agents (ed. by P. R. Saxena & R. P. Forsyth). North-Holland Publ. Co. Amsterdam, p. 349—355 1976.
6. Gordon, R.. Is pindolol effective on once or twice daily regime? Use of home blood pressure to compare three modes of administration. Abstr. Ann. Meeting Austral. Coll. Phys., Sidney p. 13 1975
7. Gugler R., Herold, W. and Dengler H. J. The effect of pindolol on exercise-induced cardiac acceleration in relation to plasma levels in man. Clin. Pharmac. Ther. 17 127 1975
8. Meier J. Pindolol. A pharmacokinetic comparison with other beta-adrenoceptor blocking agents. Acta med. Scand. Same issue p. 67—72, 1977
9. Simpson, F. O. and Waal-Manning, H. J. Hypertension and beta-adrenergic blockade. New Horizons Med. 1 39 1970.
10 Prichard B. N. C. Beta-adrenoceptor blocking drugs in angina pectoris. Drugs 7 55 1974
11 Prichard, B. N. C. Aellig, W. H. and Richardson, G. A. The action of intravenous oxprenolol, practolol, propranolol and sotalol on acute exercise tolerance in angina pectoris, the effect on heart rate and the electrocardiogram. Postgrad. Med. J. (Nov. Suppl.), 46: 77 1970.
1 Waal-Manning, H. J. & Wood A. J. b. d. versus t. d. pindolol in hypertension. Med. J. Austral. 62 274 1975

DISCUSSION

Lennart Hansson
You made a statement, Dr Aellig, that the sympathetic tone is very low in supine resting position, and for that reason there was an increase in heart rate with pindolol. If you had used a blocker without intrinsic stimulating activity you would then expect very little or no reaction in heart rate. But in fact, when you used propranolol, you showed a substantial reduction in heart rate. The disturbing fact was that the initial heart rate in the propranolol group was much higher than in the pindolol group. How do you explain that

Walter Aellig
The group of subjects was the same, but even if you administer different drugs in randomized sequence to the same subjects, there always remains a variation of the resting values.

Lennart Hansson
Yes, but the heart rate at rest was definitely higher in the propranolol group

Walter Aellig
Resting heart rate in the supine position was 83±3 beats/min before propranolol and 81±4 beats/min before pindolol. This difference is not significant.

To your second point Of course sympathetic tone is not zero in the lying position, but it is lower than in the sitting position With a similar initial heart rate in the lying position the frequency decreased after propranolol and increased with pindolol In the sitting position however resting heart rate was reduced both after propranolol and after pindolol.

Anders Vedin
I would like to comment on the effect duration of pindolol versus propranolol Patients never take single doses, but sustained medication. Therefore a more relevant comparison is to compare duration of effect after prolonged medication. We have done such study comparing the effects of 160 mg of propranolol daily versus 10 mg of pindolol daily The doses were given once daily and the patients were treated for one week. The effect on exercise induced tachycardia was studied 24 hours after the last dose The quantitative effect of propranolol was higher than that of pindolol indicating that during sustained medication the duration of propranolol is longer than that of pindolol.

Nils Svedmyr
I want to raise one further question. It has been said that pindolol has bell-shaped dose-response curve That means that higher doses produce less decrease in blood pressure, or that the lowering of a high dose can decrease the blood pressure even more From what I have seen of the literature, this statement is based only on uncontrolled studies, and I have found no proof that the dose response curve for pindolol differs from other beta-blockers.

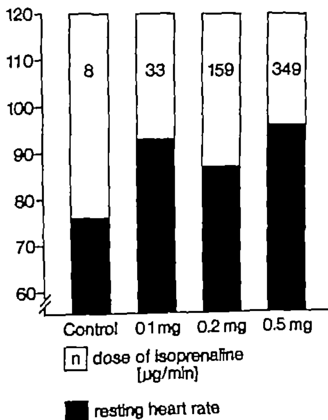


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		Before therapy	β-blocker therapy twice or 3-times daily	Pindolol once daily 12 weeks	24 weeks	36 weeks
Group I =16	Syst. BP	199±23	146±11	150±10	149±8	152±9
	Diast. BP	117±11	90±7	92±5	92±6	92±7
	Heart Rate		76±8	80±7	78±9	82±10
	Dosage mg			11,6	12,9	13 1
Group II =14	Syst. BP	189±16	147±14	147±16	150±16	151±15
	Diast. BP	115±14	86±8	88±8	87±10	88±10
	Heart Rate		65±9	65±8	73±13	71±10
	Dosage mg			13,9	13,8	13,6
Group III n=14	Syst. BP	177±24	141±15	138±15	142±16	139±15
	Diast. BP	115±8	90±6	88±10	92±9	90±9
	Heart Rate		69±12	73±9	72±11	67±7
	Dosage mg			10 7	10,8	12,1
Total	Syst. BP	189±23	145±13	145±14	147±15	147±15
	Diast. BP	116±9	89±7	89±8	91±8	90±9
	Heart Rate		70±11	73±10	75±11	74±11
	Dosage mg			12,0	12,5	13,0

Table 2. Mean (±S.E.M.) supine blood pressure (mm Hg), heart rate (beats/min) and dosage of pindolol in 44 patients completing trial I. Group I, II and III represent patients previously treated with pindolol, alprenolol or propranolol respectively. Compared with the values during therapy twice or three times daily there were no significant differences for systolic and diastolic blood pressure or heart rate when patients were transferred to a once-daily dose of pindolol.

Design of the trial

The patients had to have a supine diastolic blood-pressure (DBP) of ≧105 mm Hg registered on at least two different occasions to be enrolled in the study. After that there was a placebo-period of three weeks. Patients, whose DBP fell below 105 mm Hg during the placebo-period were to be excluded from the study. The blood-pressure at the end of the placebo-period was recorded as the initial value in the calculations.

The active treatment started with 5 mg of pindolol given orally at 8 a.m. The supine blood-pressure was measured at intervals of four weeks. The criterion for adequate control was considered to be a pressure of under 165/95. The dose of pindolol was increased—if necessary—in steps of 5 mg up to a single daily dose of 20 mg. Doses over 20 mg were not regarded as suitable in this study.

The period of active treatment covered four months. Thus, patients requiring 20 mg daily were observed for one month on that dose.

The blood-pressure was measured by the same person with the same mercury-sphygmomanometer after 10 minutes rest. The diastolic pressure was

	Age years		
	30—39	40—49	50—59
Men	2	5	3
Women		3	3

Table 3. Patients grouped according age and sex in study II. Sixteen patients.

Classi-study II.	WHO I	WHO II	FH 0	FH I	FH II
Men	7	3	5	2	3
Women	5	1	3	2	1

Table 4. Patients grouped according to WHO and to fundoscopy changes according to Keith-Wagener Barker

of the sounds. The pressure was measured between 8—9 a.m. and the patients were instructed not to take the morning dose of pindolol that day. For statistics, Student's two-tailed t-test for paired differences was used.

Results

	n
Total no in study	57
Age	
<40	9
40—59	40
≥60	8
Sex	
Men	37
Women	20
WHO Group	
I	32
II	25
Heart volume (ml/m²)	
≤500 ml	43
>500 ml	14
Duration of hypertension	
< 1 year	5
1— 2 year	31
3— 5 year	10
6—10 year	7
>10 year	4

Table 1 Patients in study 1 grouped according to WHO-classification, duration of hypertension sex and age.

tension according to WHO-criteria, heart volume as well as the duration of hypertension is shown in Table 1

The patients were *switched over to pindolol once* daily beginning with 10 mg given in the morning The pressure was checked at intervals of four weeks and if a satisfactory pressure-level, i.e a diastolic pressure at or below 100 mm Hg was not maintained the dose was increased by 5 mg at each visit up to a single dose of 20 mg.

The blood pressure was measured after 10 minutes rest in the morning, and the patient was instructed not to take the tablets that morning. In this way it was ensured that 24 hours had elapsed since the last tablet intake.

The study was carried out for 36 weeks on the once daily regime with pindolol

Results
44 patients completed the trial and constituted the basis for the statistics. In four patients, a diastolic pressure of 100 mm Hg could not be maintained even on 20 mg and those patients were excluded from the study One patient died of a myocardial infarction after 8 weeks. In four patients side-effects were registered to such a degree that the treatment had to be abandoned. For three patients the reason was vertigo after tablet intake and for one gastrointestinal troubles in the form of diarrhoea. The effects on blood pressure are shown in Table 2. It shows the initial blood-pressure, the pressure after treatment with multiple doses of beta-blockers, i.e at the start of the trial and the pressure after 36 weeks on a single daily dose of pindolol. It is seen that there is no statistical difference between the pressures before and after the trial. Compared with initial values, there were no significant differences for blood pressure or heart rate when patients were transferred to a once-daily dose of pindolol

The duration of the study—36 weeks—is certainly long enough to rule out any possibility of a carry-over-effect from the previous treatment However it is of course only shown, that it is possible to maintain an adequate pressure-control with pindolol once daily in patients already treated with multiple doses of beta-blockers. Therefore, a further study was carried out, starting with a single dose of pindolol from the beginning of the treatment of the hypertension

STUDY II

Material and methods
Sixteen out-patients with mild to moderate previously untreated essential hypertension were selected for the study They were all included in the routine examination scheme including ECG, fundoscopy chest x ray determination of electrolytes and creatinine in serum and analysis of urine for protein, glucose and blood-cells. If necessary further investigations were carried out, such as intravenous pyelogram, angiography and hormone analysis

The age and sex distribution is shown in Table 3 In Table 4 the patients have been grouped according to the WHO-criteria of hypertension as well as to the fundoscopy changes according to Keith Wagener Barker

The usual contraindications for treatment with beta-blockers were considered

scription of a long acting diuretic, which can also be administered once daily in order to preserve the benefits of a simple regime. This matter however needs further investigation. The material is too small to draw any certain conclusions regarding the side-effects. It is worth noting that no patients had sleep disturbances or nightmares. This is in line with earlier observations on once a day dosage (8) and perhaps these well known side-effects can be reduced when the tablets are given only in the morning.

No undesired beta-blocker-induced bradycardia was observed. As pindolol has an intrinsic sympathomimetic effect this complication is most unlikely to appear even on high doses of the drug. In a study like the present one, which is not performed with a strict double-blind technique the bias-risk has to be considered. However the aim has been to investigate a simple treatment and not to prove the hypotensive effect of pindolol, which is already documented. Furthermore it is debatable whether there is any possibility of performing a strict double-blind trial with beta-blockers, in view of their effect on the pulse rate both at rest and during work.

Summarizing, the once daily dosage regime with pindolol seems to be a simple and effective way to treat mild to moderate hypertension with relatively few side-effects. It offers advantages, both for the patient and the physician, which are of great importance in view of the life-long duration of the therapy

REFERENCES

1. Amnecker et al The relationship of plasma levels of pindolol in hypertensive patients to effects on blood pressure, plasma renin and plasma noradrenaline levels Clin Exp Pharm Physiol 2. 203 1975
2. Caldwell, J R et al The dropout problem in antihypertensive treatment J Chron Dis 22. 579 1970.
3. Frithz, G Hood, B Hansson, L. & Björk, S.. Cerebrovascular lesions Active antihypertensive treatment and the present situation. Acta Med Scand 196. 35, 1974
4. Frithz, G.. Pindolol once daily in the treatment of hypertension. Läkartidningen 72. 3073 1974
5. Gordon, R.. Is Pindolol effective on a once or twice daily regime? Use of home blood pressures to compare three modes of administration. Royal Australian College of Physicians An Meeting Sydney 21—23 May 1975
6. Hansson, L., Hood, B., Malmcrona, R., Olander R Rosenhall, L., Westerlund, A.. Åberg, H.. Långtidsbehandling av hypertoni hos 158 patienter med propranolol Läkartidningen 68 3517 1971
7. Malahy B.. The ffect of instruction and labelling on the number of medication errors made by patients at home. Am J Hosp Pharm 23 283 1966.
8. Danielson, M Frithz, G Malmborg, R., Nordstrom-Öhrberg, G., Schröder G Long term blood pressure control with pindolol given once daily To be published.
9. Olsson, S. & Varnauskas, E Duration of betareceptor blockade after oral administration of LB 46. Europ J Clin Pharmacol 5. 214 1975.
10. Prichard, B. N C. & Gillam, P M S.. The use of propranolol in the treatment of hypertension. Brit Med J 2 725 1964

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Table 5 *Mean* (±S.E.M.) supine blood pressure (mm Hg) before and after 4 months treatment Pindolol dose in 4th month Sixteen patients.

	Before treatment	After treatment	p
Systolic BP	181.2±7.1 (210 —170)	150.1±8.3 (165 —120)	<0.001
Diastolic BP	110.5±3.2 (120 —105)	91.0±3.0 (100 —80)	<0.001
Dose in 4th month	10 mg	15 mg	20 mg
WHO I patients	3	7	2
WHO II patients		1	3

No one had to be excluded due to a normalized pressure after the placebo period Fourteen achieved the criteria set for satisfactory pressure-control, i.e a pressure of <165/95 mm Hg. The two patients, who did not reach that level both belonged to the WHO II group and had a diastolic pressure of 100 mm Hg after four months, i.e after one month on 20 mg pindolol. The results after *four months treatment* are shown in *Table 5* as well as the dosages of pindolol at that time It may be observed that the mean dosage of pindolol is somewhat lower for patients belonging to the WHO-I group than that for the WHO-II group

Side-effects

Three patients reported side-effects, for which pindolol may have been responsible. One patient complained of palpitations, one of dizziness and one of slight nausea after taking the tablets. The first two patients were receiving 15 mg, the last one 20 mg. No one reported sleep-disturbances.

DISCUSSION

The study demonstrates the possibility of treating previously untreated hypertensive patients, starting with one single daily dose of pindolol.

It is reasonable to assume that this form of treatment should be restricted to milder forms of hypertension From Table 5 it can be concluded that the smallest *effective* dose *is 10 mg. It is al*most certain, that this dose can be given directly without a previous running-in period with 5 mg. As the mode of tolerance to the single dose therapy was not known at the start of the study this design was chosen. However a further study now in progress indicates the possibility of starting even with 15 mg directly

On the other hand it should perhaps also have been possible to go further than 20 mg in one single dose However *it was judged as not advisable* due to the possibility of subjective symptoms. Therefore after the study was ended it was considered preferable to treat the two cases who did not achieve a fully acceptable pressure-control on pindolol alone with a combination of a single daily dose of pindolol with one tablet of the fixed *combination of 50 mg hydrochlorothiazide and 5* mg amiloride (Moduretic®) given simultaneously On that combination both patients achieved a diastolic pressure of 90 mm Hg after one month's further treatment.

The blood-pressure was measured in the morning to obtain an interval of 24 hours from the last tablet intake. *It could naturally be argued that it* is of more interest to measure the pressure during the day in the activities of daily life. However it is well established that the effect of a peroral dose of pindolol reaches its peak after about 3—4 hours (1) so there is little reason to believe, that the pressure-control should be less satisfactory during *the day Furthermore it has recently been shown* by Gordon (5) who treated patients who cooperated in measuring their own blood-pressures during the day that there were little differences in the over all pressure-control whether pindolol was administered once twice or three times daily

The difficulties of maintaining patients with *known hypertension on continous treatment* are documented in many studies (2 3). It is also known that the chances of missing tablet intakes increase as the dosage *frequency* increases (7). Therefore the administration of pindolol once *daily can be useful in helping patients to comply* with the prescribed treatment. *If* an adequate response is not obtained on a tolerable dose of the beta-blocker it is reasonable to suggest the copre-

scription of a long acting diuretic, which can also be administered once daily in order to preserve the benefits of a simple regime. This matter however needs further investigation. The material is too small to draw any certain conclusions regarding the side-effects. It is worth noting that no patients had sleep disturbances or nightmares. This is in line with earlier observations on once a day dosage (8) and perhaps these well known side-effects can be reduced when the tablets are given only in the morning.

No undesired beta-blocker-induced bradycardia was observed. As pindolol has an intrinsic sympathomimetic effect this complication is most unlikely to appear even on high doses of the drug. In a study like the present one, which is not performed with a strict double-blind technique, the bias-risk has to be considered. However the aim has been to investigate a simple treatment and not to prove the hypotensive effect of pindolol, which is already documented. Furthermore it is debatable whether there is any possibility of performing a strict double-blind trial with beta-blockers, in view of their effect on the pulse rate both at rest and during work.

Summarizing, the once daily dosage regime with pindolol seems to be a simple and effective way to treat mild to moderate hypertension with relatively few side-effects. It offers advantages, both for the patient and the physician, which are of great importance in view of the life-long duration of the therapy.

REFERENCES

1. Aarvekar et al. The relationship of plasma levels of pindolol in hypertensive patients to effects on blood pressure, plasma renin and plasma noradrenaline levels. Clin Exp Pharm Physiol 2: 203, 1975.
2. Caldwell, J. R. et al. The dropout problem in antihypertensive treatment. J Chron Dis 22: 579, 1970.
3. Frithz, G., Hood, B., Hansson, L. & Björk, S. Cerebrovascular lesions. Active antihypertensive treatment and the present situation. Acta Med Scand 196: 35, 1974.
4. Frithz, G. Pindolol once daily in the treatment of hypertension. Läkartidningen 72: 3073, 1974.
5. Gordon, R. Is Pindolol effective on a once or twice daily regime? Use of home blood pressures to compare three modes of administration. Royal Australian College of Physicians. An Meeting Sydney 21—23 May 1975.
6. Hansson, L., Hood, B., Malmcrona, R., Olander R., Rosenhall, L., Westerlund, A., Åberg, H. Långtidsbehandling av hypertoni hos 158 patienter med propranolol. Läkartidningen 68: 3517, 1971.
7. Malahy, B. The effect of instruction and labelling on the number of medication errors made by patients at home. Am J Hosp Pharm 23: 283, 1966.
8. Danielson, M., Frithz, G., Malmborg, R., Nordström-Öhrberg, G., Schröder, G. Long term blood pressure control with pindolol given once daily. To be published.
9. Olsson, S. & Varnauskas, E. Duration of beta-receptor blockade after oral administration of LB 46. Europ J Clin Pharmacol 5: 214, 1975.
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Future Development in the Field of Hypertension

Chairman Bernt Hökfelt

Department of Endocrinology General Hospital Malmö, Sweden

Generally speaking the future developments in hypertension as applied to clinical medicine and health care will depend on how successful research will be in further exploring etiology and pathogenesis, and in producing efficient and safe diagnostic procedures and therapy Of equal importance is the extent to which presently known and future diagnostic procedures and therapeutic means will be made available and used. These developments are partly the direct responsibility of the medical profession in a broad sense, but partly that of political decision-makers and administrators, for whom correct information based on knowledge and good advice from the medical expertise are of fundamental importance. The importance of the knowledge must be stressed in view of the present trends amongst politicians and others to overlook this absolute prerequisite for meaningful and successful health care, including preventive medicine.

Needless to say the future developments in the field of hypertension will be based on, and closely linked to the present and the past. Accordingly it might be appropriate to paint a background to the papers to follow by recalling some of the major events and progresses within hypertension research over the last three decades.

The wellknown American investigator Irvine Page at the end of the 1940-s proposed what he named the mosaic theory of hypertension.

According to this theory all the various components which influence blood pressure must be in equilibrium to maintain appropriate blood pressure and adequate tissue perfusion. If one factor changes and becomes dominant, the others will adjust accordingly This theory has served as an inspiring and constructive model. The

various interdependent facets when placed in the corners of an oc tagon, make possible to visualize the great number of points at which blood pressure control can be interfered with and deranged—but also influenced therapeutically (Figure 1).

It might be worth while pointing out that the mosaic concept im plies that hypertension principally is a disorder of blood pressure regulation which means that hypertension is induced via mecha nisms, normally acting to maintain normotension Accordingly the more we learn about physiological blood pressure and perfusion control and the various factors involved, the better we will under stand the pathology of hypertensive disease.

It is gratifying to be able to state that the functional dependence and the integration of several of the facets covered in the octagon have been explored and even defind during the years after the pre sentation of the mosaic theory In particular I would like to remind you of three major components:

1) In the middle of the fifties we witnessed the isolation chemical identification and synthesis of aldosterone the exponent for the physiologically so important mineralocorticoids but also the im mediate cause of hypertension as documented in Conn s syndrome and other forms of primary aldosteronism. It has also become evident that aldosterone often is engaged secondarily in other forms of hypertension at various stages, such as renovascular hypertension phiochromocytoma primary reninism and malignant hypertension From therapeutic point of view the discovery of aldosterone and the clarification of its role in disease led to the synthesis of widely used therapeutic agents such as the aldosterone antagonist spironolactone

2) The discovery in 1898 by Tigerstedt and Bergman, that the kidney produces a hypertensive principle remained a scientific enigma until Brown Menendez, Helmer Page and others demonstrated that renin is an enzyme inducing the production in the body of the very active vasoconstrictor peptide angiotensin which was isolated, struc turally defined and synthesized, again events which happened in the middle of the fifties.

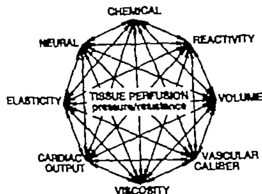


Fig. 1 The "Mosaic Theory"

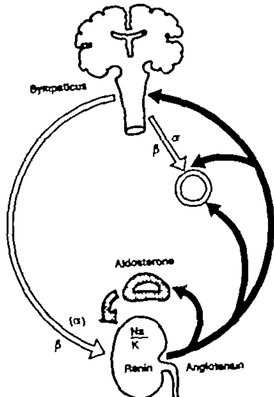


Fig. 2. Influence of angiotensin on blood pressure.

Further research has clearly established that angiotensin plays a physiologically important role as a constrictor agent under certain conditions and also that it plays a role as a stimulator of aldosterone production in health and disease The hypertensive potential of renin-angiotensin has been convincingly demonstrated in cases of primary reninism and also in certain types of renovascular hyper tension induced experimentally in animals and occurring spon taneously in man. There is also good evidence that angiotensin can influence blood pressure by increasing sympathetic activity via stimulation at the nerve endings and centrally (Figure 2).

3) Discoveries of fundamental importance have been made concerning the mediation of sympathetic function peripherally and centrally and with respect to the anatomical distribution of cate cholaminergic neurons within the central nervous system. Suffice is to mention the concept of alpha and beta-adrenergic receptors published by Ahlqvist 1948 the demonstration of centrally located noradrenergic, dopaminergic and lately adrenergic neurons, and the presence centrally of alpha and beta-receptor mechanisms engaged in the regulation of blood pressure.

It has also become evident that not only does the renin-angiotensin system influence the activity of the sympathetic nervous system, as mentioned above, but that the sympathetic nervous system exerts a pronounced effect in stimulating renin secretion by the juxtaglomerular cells in the kidney Accordingly sympathetic activity constitutes a determinant for the production of renin-angiotensin,

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New Trends in Pharmacology

Matts Henning

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Abstract. Among the factors influencing the arterial blood pressure the neural control through the autonomic nervous system is of paramount significance. The sympathetic division of this system holds a key position in this regard and its neural transmission mechanisms represent well established target for pharmacological interference aimed at lowering blood pressure. This presentation will first deal with the morphological and physiological basis for blood pressure control through the sympathetic nervous system and the various possibilities for antihypertensive drug action through this system. Special attention will be drawn to recent advances in catecholamine research which may offer new leads in the development of blood pressure lowering agents. A second topic in this review will be some remarks on other pharmacological principles for interference with vascular control apart from the sympathetic system, particularly the vasodilator principle.

I CATECHOLAMINE MECHANISMS IN BLOOD PRESSURE REGULATION

As previously mentioned, the role of the peripheral sympathetic system and its neural transmission mechanisms in circulatory homeostasis is comparatively well recognized The central nervous mechanisms determining the activity of the sympathetic system are considerably less understood. As will be shown later an increasing body of evidence indicates that central catecholamine (CA) neurons participate in cardiovascular control.

There is ample evidence for a transmitter function of the CA, dopamine (DA) and noradrenaline (NA) (5). These neurons have their cell bodies located in the lower brain stem (medulla oblongata, pons and mesencephalon) while their terminals are distributed to nearly all parts of the brain and the spinal cord although with varying density A number of CA pathways have been mapped, e.g. descending NA pathways from the medulla oblongata to the sympathetic centers in the spinal cord, ascending pathways from the brain stem to e.g. the hypothalamus and the preoptic area. This distribution is suggestive of a functional influence on central autonomic mechanisms. Within the brain stem are found short NA neurons which seem to innervate i.a. brain stem autonomic centers—again providing a morphologic background for central CA s regulating central autonomic function and hence the cardiovascular system.

Direct evidence for central CA mechanisms being involved in cardiovascular control has emerged from pharmacological studies utilizing CA amino acid precursors in combination with selective inhibitors of various steps in CA biosynthesis (20). The use of so called peripheral decarboxylase inhibitors has been of particular interest since they inhibit the enzyme activity only outside the central nervous system thus permitting a separation of central and peripheral actions. The CA precursor L 3 4-dihydroxyphenylalanine (L-dopa) produces a hypertensive response in the conscious rat (22). This is abolished or after a large dose of L-dopa converted into a hypotensive response when the enzyme dopa-decarboxylase is inhibited in peripheral tissues. The hypotensive effect is abolished when dopa-decarboxylase is inhibited both centrally and peripherally by other compounds entering the central nervous system, demonstrating that the lowering of blood pressure is mediated by an action of CA formed from L-dopa in the central nervous system. These results have been amply verified in several animal species (see 21) but no conclusive data from human experi-

resulting in effects on blood pressure regulation via a direct influence on the vessels but also via aldosterone production. Sympathetic amines, renin-angiotensin and aldosterone in reality have been found to function as a unit of physiological importance for blood pressure regulation but also contributing to hypertension of various kinds at various stages. Under certain conditions this functional integration actually constitutes a vicious circle.

As a result of new discoveries concerning renin-angiotensin and also sympathetic nervous function new agents have been produced of diagnostic and therapeutic potential such as converting enzyme inhibitor and competetive inhibitors of peripheral angiotensin action—not to mention all the compounds that have been made available to influence sympathetic function centrally and peripherally

Using the complex mosaic theory as a background, I have tried to present some advances within a rather limited field but which actually represent a rather magnificent development.

We have touched upon neural, humoral and hormonal mechanisms of general importance for vasoconstriction salt balance volume regulation and peripheral resistance. No doubt, future research will lead to new discoveries within these areas. At the present time great interest is still focused on central and peripheral sympathetic mechanisms but in addition the field is expanding to include dopaminergic and serotoninergic neurons the parasympathetic system and also the newly discovered field of putative transmittors of peptide nature such as enkefalin and substance P which undoubtedly will be found to play a role in central blood pressure regulation. In the meantime many investigators are engaged in the search for a sodium excreter the so called third factor which some believe to be related to bradykinin or other kinins or prostaglandins, known to be extremely active as vasodilators but also as promotors of sodium and water excretion From discussions at this symposium it has been made clear that the hyperkinetic state of early essential hypertension mostly is *not* hyperkinetic but rather an expression of a metabolic disturbance the nature of which awaits exploration thus another area for future research

In connection with theories on the mechanism of action of clonidine much interest has recently been paid to the relevance of so-called presynaptic receptor mechanisms. The first indications of such mechanisms came from studies on the effects of NA receptor blocking agents on CA turnover: it was found that the utilization of CA appeared to be increased in the presence of CA receptor blocking agents (11). It was also soon found that CA receptor agonists, e.g. clonidine, caused a decrease in CA utilization (6). These observations have been confirmed both in peripheral and in central nervous CA neurons. Apparently the CA released by neuronal activity once it reaches a threshold concentration in the synaptic gap activates presynaptic receptors, probably located on the nerve ending which then trigger a negative feedback mechanism which slows down synthesis and release of the CA transmitter (3 12). There is now ample evidence for the existence of presynaptic receptors or autoreceptors as they are perhaps more aptly designated in both peripheral and central nervous CA neurons. They may be of the α-type, mediating a retardation of CA synthesis and release but probably also of the β type which may be activated by low concentrations of CA and lead to an increase in the CA transmitter output (3 12). To complicate the matter further there are also indications of presynaptic muscarinic inhibitory receptors in at least peripheral CA nerve endings. The ubiquitous prostaglandins have also been reported to influence CA release. prostaglandins of the E series inhibit NA release in peripheral tissues (32)

The functional significance of these autoreceptors in drug action is by no means clarified but it is of interest that clonidine has a much higher affinity to these receptors than to the "classical" post-synaptic α-receptors in the peripheral sympathetic system. Also, certain biochemical presynaptical clonidine effects occur in the same dose range as that required to lower blood pressure in animals (4). It may therefore be that clonidine, in certain dose ranges, owes its hypotensive properties to an action on presynaptic CA receptors. On the other hand, clonidine facilitates the vagally mediated cardiodepressor reflex and this action has been shown to be independent of NA release from central neurons, clearly showing direct stimulation of postsynaptic NA receptors (24). Thus, this issue is far from settled and furthermore, the clinical implications are obscure although it may be that it has bearing on interactions between clonidine and other drugs acting at central CA receptors. Neuroleptic agents of the phenothiazine type exemplify this: animal studies suggest that they may counteract the hypotensive effect of clonidine but clinical pharmacological studies to this effect have not been performed. The tricyclic antidepressants also have profound effects on central CA mechanisms and, again, animal experiments that show antagonistic effects towards the antihypertensive effect of clonidine are available but the clinical counterpart is lacking (see 35). The observation that α-adrenergic blocking agents such as tolazoline completely abolish the hypotensive effect of clonidine in man (9) is a clinical counterpart to the pharmacological studies previously mentioned indicating a central nervous action of clonidine on α-receptors in man.

From practical point of view centrally acting antihypertensive drugs like methyldopa and clonidine offer certain advantages, particularly when compared to peripheral sympathetic neurone blocking agents such as guanethidine and bethanidine. Thus, methyldopa and clonidine cause considerably less orthostatic side-effects than the peripherally acting drugs and other signs of sympathetic blockade e.g. failure of ejaculation are rarely seen in patients receiving methyldopa and clonidine (for references see 15 19). However both these drugs produce a sedative effect, which represents a major drawback in their clinical usage. This effect is probably correlated to an interference with central CA mechanisms involved in the maintenance of i.a. wakefulness (26) and may be inherent in the principle of action of these drugs

New developments in the field of centrally acting antihypertensive drugs include several structural analogues of clonidine; so far all drugs in this category subjected to clinical trials have displayed a similar profile of side-effects as clonidine, i.e. a sedative effect. Some examples of such agents are guanabenz (30) and BS 100-141 (23). It would appear that more information must be sought with regard to structure-activity relationships of these central NA receptor agonists. There exists the possibility that the receptors mediating a decrease in sympathetic activity may have dif

ments seem to be available. It has been suggested that the occurrence of orthostatic hypotension during L-dopa treatment of patients with Parkinson s disease is of central origin and analogous to the hypotensive effect observed in animal experi ments. However the use of combinations of L-dopa and peripheral decarboxylase inhibitors in treating Parkinsonian patients does not always re duce the incidence of orthostatic reactions.

The hypotensive action of L-dopa has been subject to further analysis and results from several different research groups indicate that the effect is mediated by activation of central NA receptors, most likely located in the lower brain stem (21) The occurrence of NA nerve terminals in this region as well as its key position in blood pressure regulation should be noted in this connection. Thus, the nucleus of the tractus solitarius and the dorsal nucleus of the vagus, both of which participate in the central mediations of baroreceptor reflexes, show a high density of CA terminals. Furthermore, bilateral lesions of these structures result in a severe hypertension and alterations in CA metabolism in the central nervous system (14)

2. CENTRAL CATECHOLAMINE MECHANISMS AND ANTIHYPERTENSIVE DRUG ACTION

Studie aimed at elucidating the mode of action of L-α 3 4-dihydroxyphenylalanin (methyldopa) provided the earliest indications of central CA regulation of blood pressure. This subject has been re viewed in detail elsewhere (19) In summary the most convincing arguments against the so-called "false transmitter" theory came from studies of the interaction between methyldopa and a peripheral decarboxylase inhibitor which was shown to prevent the synthesis of false transmitters from methyldopa in the peripheral sympathetic system while not influencing the antihypertensive action of this drug. On the other hand, this action is abolished following decarboxylase inhibition in both the peripheral and the central nervous system These observation gave clear indication that the antihypertensive action of methyldopa is me diated by its CA decarboxylation products in the central nervous system. Subsequent analysis using i.a. inhibitors of the formation of NA from DA have demonstrated that methyl-NA is implicated apparently acting by direct stimulation of NA receptors. As in the case of L-dopa, these receptors are probably located in the brain stem (20 21)

Little attention has been paid to the possible relevance of these observations in the clinical use of methyldopa in hypertensive patients. This is somewhat surprising since non toxic peripheral decarboxylase inhibitors are currently available, being used in conjunction with L-dopa in the treat ment of Parkinson s disease. Apart from the in direct evidence provided by the various well known central nervous side effects of methyldopa in man only one report is available which indi cates a central site of attack (31) The experiment, performed on a single patient, is a direct parallel to the animal studies referred to above studying the influence of peripheral decarboxylase inhibition on the antihypertensive action of methyldopa. As in animal experiments, this was found to be unaffected in spite of a pronounced decrease in the formation of methyldopa decarboxylation products. From the pharmacodynamic point of view a controlled study in a larger group of pa tients would be necessary before the results from animal experiments can be extended to man.

There is general agreement among pharmacologists that the antihypertensive effect of clonidine is mediated largely by an action in the central nervous system (35). In animal experiments, clonidine is also an effective agonist at central nervous NA receptors and agents known to block these re ceptors also prevent the cardiovascular effects of clonidine (35). It is therefore conceivable that the hypotensive action of clonidine results from an ac tivation of central NA receptors. These receptors are usually classified as belonging to the α type since clonidine has α adrenergic effects in peripheral tissues and since the NA receptor antagonists which block the central actions of clonidine also are peripheral α-adrenergic blocking agents. As in the case of L-dopa and methyldopa the re ceptors mediating the hypotensive response to clonidine seem to be located in the lower brain stem. However there are also indications that clonidine influences blood pressure at suprabulbar levels in the brain. Thus, actions of clonidine in the posterior hypothalamus may contribute to the hypotensive effect and there is also evidence that hypothalamic and/or cortical NA mechanisms influenced by clonidine may mediate blood pressure increasing actions (34).

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ferent characteristics from those causing the sedative effect, allowing for a greater selectivity in agonist action. Future research in this field could follow such lines.

The β-receptor blocking agents represent a novel approach to anti-hypertensive therapy and their mechanism of action is a challenge to pharmacologists. Various peripheral actions such as baroreceptor resetting cardiac effects, decreased renin secretion have been held responsible for their anti-hypertensive property but do not provide a satisfactory explanation (review in 1) There is by now a fairly large number of studies which suggest that β-blocking drugs may act by influencing CA mechanisms.

First, it has been demonstrated in animal experiments that propranolol diminishes the effect of vasoconstrictor nerve stimulation without decreasing the sensitivity infused NA (2). Secondly the release of NA from sympathetic vasoconstrictor nerves is decreased after β receptor blockade (1) Third there is a significant decrease in the vasoconstrictor nerve function in spontaneously hypertensive rats after long-term treatment with propranolol and metoprolol (27) All these observations could be explained by a blockade of presynaptic receptors of the β type in peripheral sympathetic nerves (27). As previously mentioned these receptors seem to mediate an increase in the release of NA and their blockade would then of course diminish the output of NA. Clinically it has been reported that the urinary output of NA is reduced during therapy with a β-blocker (16)

Finally it should be mentioned that a number of investigators have found evidence that central nervous effects of β receptor blocking drugs may participate in mediating the decrease in blood pressure (13). This theory is largely based upon experiments involving local administration of β-blocking agents into the brain tissue or the cerebral ventricles and therefore not immediately transferable to the clinical situation. Somewhat more convincing are the observations that intravenous infusion of propranolol into conscious animals leads to a reduction in the electrically recorded activity in sympathetic nerves (25). Considerable more work is required before this question is settled

With regard to future developments in the field of β-receptor blockade there is little doubt that the cardioselective (β_1) receptor blocking agents have come to stay Although there is evidence that the subdivision of β-receptors is less strict than previously thought clinical experience clearly shows that β_1-selective blockers offer considerable advantages in for example treating hypertensive patients with bronchial obstruction. These blockers also have the haemodynamic advantage over the non-selective type that β_1-selective blockade leaves the endogenous β_2-receptor mediated vasodilator effects unopposed, which may contribute to the blood pressure lowering effect of the β_1-selective blockers (29). However administration of salbutamol to practolol treated hypertensive patients gave no further fall in blood pressure (7). Non-selective blockers with intrinsic betamimetic activity could theoretically lead to a somewhat similar haemodynamic pattern and there are clinical observations which support this theory (Atterhög, Dunér & Pernow this symposium).

On the other hand, this type of non-selective blockers will produce a smaller decrease in cardiac output than a blocker without intrinsic activity (29) Since a majority of the hypertensive population have an increase in peripheral vascular resistance, there is an obvious need for a vasodilator component in the therapeutic regimen. This may of course be accomplished by the use of vasodilator drugs in a combination therapy with β-blocking agents but practical complexities call for drugs combining β-blocking and vasodilatory properties. At least one such drug, labetalol (AH 5158) has been given fairly extensive clinical trial (33) This agent combines non-selective β-receptor and α-receptor blocking effects, thus influencing both cardiac output and vascular resistance.

Although orthostatic reactions do not seem to have been a major problem in the use of labetalol it should be pointed out, that blockade of the α-receptors always implies a potential risk of orthostatic blood pressure fall. It appears that careful titration of dosage decreases this risk in the case of labetalol. Another approach to increase the antihypertensive effect of β-blocking drugs would be to combine β-blockade with a selective vasodilatory action on resistance vessels, such compounds have been synthesized but are still largely at the pre-clinical stage of development. At present time the prescribing physician has to resort to giving

the β-blocking and the vasodilator drug as separate formulations.

3. VASODILATOR DRUGS

Vasodilator drugs for use in antihypertensive treatment should influence resistance vessels selectively: any dilating effect on capacitance vessels will imply a theoretical possibility for orthostatic reactions. As mentioned above, α-receptor blockade carries this risk and can never be used as the sole principle in antihypertensive therapy. Dilatation of the resistance vessels will lower total vascular resistance and, therefore, blood pressure, but will also trigger a number of reflex adjustments aimed at counteracting the fall in blood pressure. These mechanisms include increase in cardiac output, increased secretion of renin and hence a state of hyperaldosteronism, all of which seriously limit the usefulness of vasodilator drugs as single agents in the treatment of hypertension (cf Hansson, this symposium). It has been claimed that some of these agents are less liable than others to cause e.g. sodium retention (as a consequence of the previously mentioned reflex mechanisms), but a critical evaluation shows no major differences in this respect. Some of the currently available vasodilators are not exerting a single action, i.e. dilatation of the resistance vessels. Thus, prazosine which has received extensive clinical trials also tends to produce a slight α-receptor blockade, particularly at higher dosage and leading to orthostatic side-effects. It has been shown, that this problem may be partly overcome by careful titration of dosage and employing the smallest possible doses, particularly at the onset of prazosine treatment (18).

An interesting class of pharmacological agents may constitute a new principle for the therapy of arterial hypertension, although these drugs are currently used for other purposes. These drugs interfere with the transport of calcium ions at one or several stages in the handling of these ions by various cells. Vascular smooth muscle, like striated muscle and myocardial muscle is highly dependent on the availability of calcium ions, which serve to mediate the coupling between excitation and contraction. Calcium ions, liberated from intracellular storage sites take part in the interaction between the contractile elements of the muscle and pharmacological agents interfering with these processes may profoundly influence the excitation-contraction coupling. This has been demonstrated for both myocardial and vascular preparations in vitro (17) and probably represents the basic mechanism underlying the effects of these drugs in man. Verapamil is perhaps the best known representative for this class of drugs: calcium antagonism will lead to e.g. a decrease in myocardial oxygen consumption and a beneficial effect in angina pectoris. In addition, verapamil influences the conduction system of the heart, notably the specialized, calcium-dependent mechanisms in the atrioventricular node providing a basis for its action on certain types of cardiac arrythmias. There are now several reports indicating a therapeutically useful effect of verapamil in cases of arterial hypertension (10) but as expected with a high incidence of effects on cardiac conduction. Another recently introduced powerful calcium antagonist, nifedipine, has also been reported to be effective in lowering pressure in hypertensive patients (8) but again, complicating actions from the myocardium are to be expected. Since the most distal resistance vessels which seem to function as "pace-maker" cells in the maintenance of myogenic vascular tone are probably more dependent on calcium availability it is theoretically possible to envisage a dose of e.g. nifedipine which only affects resistance vessel tone and leaves myocardial function intact. However it should be emphasized that this principle for antihypertensive is still at its early experimentative stage and experience from clinical materials is very much limited. The problem of possible reflex adjustments resulting from the lowering of vascular resistance has not been evaluated so far and it should be pointed out that a concomitant therapy with β-blocking drugs may present hazards, these drugs also affect intracellular calcium movements resulting in a synergistic action with the calcium antagonistic agents. Serious complications (e.g. circulatory collapse or cardiac arrest) have been reported after combinations of β-blocking drugs and verapamil. Much additional evaluation is required before allowing any conclusions regarding the position of calcium antagonists in the treatment of hypertension.

REFERENCES

1. Ablad, B., Carlsson, E., Dahlöf, C. & Ek, L. Some aspects on the pharmacology of adrenergic

β-receptor blockers. In. Pathophysiology and management of arterial hypertension. Ed. Berglund G Hansson, L. & Werkö L. A. Lindgren & Söner AB Mölndal, Sweden 1975

2. Åblad, B Ek, L. Johansson, B. & Waldeck, B Inhibitory effect of propranolol on the vasoconstrictor response to sympathetic nerve stimulation. J Pharm. Pharmac. 22. 627 1970.

3 Adler-Graschinsky E. & Langer S Z.. Possible role of a β-adrenoceptor in the regulation of nor adrenaline release by nerve stimulation through a positive feed-back mechanism. Br J Pharmacol. 53 43 1975

4 Andén, N E. & Strömbom, U Stimulation of central adrenergic alpha receptors by L-dopa, α-methyldopa and clonidine. In. Central action of drugs in blood pressure regulation. Ed. Davies, D S. & Reid J L. Pitman Medical Publishing Co. Ltd. Tunbridge Wells, Kent 1975

5 Andén, N E. Carlsson, A. & Häggendal J Adrenergic mechanisms. Ann. Rev Pharmacol. 9 119 1969

6. Andén, N E., Corrodi, H. Fuxe K., Hökfelt B Hökfelt, T Rydin T & Svensson, T Evidence for a central noradrenaline receptor stimulation by clonidine. Life Sci. 9 513 1970

7 Andersson, O & Berglund, G Antihypertensive effect of β-1-receptor blockade and β-2-receptor stimulation in essential hypertension. Acta med. Scand. 197 495 1975

8 Aoki, K. Yoshida, T Kato S Tazumi, K. Sato I Takikawa, K. & Hotta K.. Hypotensive action and increased plasma renin activity by Ca^{++} antagonist (Nifedipine) in hypertensive patients. Jap. Heart J 17 479 1976.

9 Bock, K. D Merquet, P Brandt, T & Murata T.. Experimental studies with clonidine hydrochloride in normotensive and hypertensive subjects In. Catapres in hypertension. Ed Conolly M. E., Butterworths, London 1970.

10. Brittinger W D Schwarzbeck, A. Wittenmeier K. W Twittenhoff W D Stegaru, B Huber W Ewald, R. W v Henning, G E. Fabricius, M. & Strauch, M. Klinisch-experimentelle Untersuchungen über die blutdrucksenkende Wirkung von Verapamil. Dtsch. med. Wschr 96. 187 1970.

11 Carlsson, A. & Lindqvist, M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta pharmacol. toxicol. 20: 140 1963

12. Carlsson, A. Kehr W., Lindqvist M., Magnusson, T & Atack, C. V Regulation of monoamine metabolism in the central nervous system. Pharmacol. Rev 24 371 1972.

13 Day M D & Roach, A. G Central adrenoreceptors and the control of arterial blood pressure Clin. Exp. Pharmac. Physiol. 1 347 1974

14 Doba, N & Reis, D J Role of central and peripheral adrenergic mechanisms in neurogenic hypertension produced by brain stem lesions in the rat. Circulation Res. 34 293 1974.

15 Dollery C. T & Bulpitt, C. J Alpha-methyldopa. In Central action of drugs in blood pressure regulation. Ed. Davies, D S. & Reid, J. L. Pitman Medical Publishing Co. Ltd., Tunbridge Wells, Kent 1975

16. Esler M. D & Nestel, P J Evaluation of practolol in hypertension. Effects on sympathetic nervous system and renin responsiveness. Br Heart J 35 469 1973

17 Fleckenstein, A., Döring, H. J., Janke, J. & Byon, K. Y.. Basic actions of ions and drugs on myocardial high-energy phosphate metabolism and contractility Hdb. exp. Pharmak. 16. 345 1975.

18 Graham R. M. Thornell, I. R., Gain, J M., Bagnoll, C. Oates H. F & Stokes, G. S.. Prazosin: the first dose phenomenon. Br Med. J 2: 1293, 1976.

19 Henning, M.. Studies on the mode of action of α-methyldopa. Acta physiol. scand. suppl. 322, 1969

20 Henning, M.. Receptor regulation studies: significance of central catecholamine receptors in cardiovascular control. In. Frontiers in catecholamine research. Ed. Usdin E. & Snyder S. S. Pergamon Press, New York 1973

21 Henning, M Central sympathetic transmitters and hypertension. Clin. Sci. Mol. Med. 48. 195s 1975

22. Henning, M. & Rubenson A.. Central hypotensive effect of L 3 4-dihydroxyphenylalanine in the rat J Pharm. Pharmacol. 22. 553 1970.

23. Jäätelä, A. Comparison of BS 100—141 and Clonidine as Antihypertensive Agents. Eur J Clin. Pharmacol. 10: 73 1976.

24 Kobinger W & Walland, A.. Facilitation of vagal reflex bradycardia by an action of clonidine on central α-receptors. Eur J Pharmacol. 19 210. 1972.

25 Lewis, P J & Haeusler G. Central nervous effects of β-blockers in hypertension. In. Pathophysiology and management of arterial hypertension. Ed. Berglund, G Hansson L. & Werkö, L. A. Lindgren & Söner AB Mölndal, Sweden 1975.

26. Lidbrink, P The effect of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Brain Res. 74 19 1974

27 Ljung, B Ablad B Dahlöf C. Henning, M. & Hultberg, E. Impaired vasoconstrictor nerve function in spontaneously hypertensive rats after long-term treatment with propranolol and metoprolol. Blood Vessels 12: 311 1975

28 Muscholl E. Regulation of catecholamine release The muscarinic inhibitory mechanism. In: Frontiers in catecholamine research. Ed. Usdin, E. & Snyder S. S. Pergamon Press, New York 1973.

29 Sannerstedt, R.. Haemodynamic effects of adrenergic β-receptor blocking agents in arterial hypertension. In. Pathophysiology and management

of arterial hypertension. Ed. Berglund G Hansson, L. & Werkö, L. A Lindgren & Söner AB Mölndal, Sweden 1975.

30. Shah, R. S Walker B R., Vanov S. K, & Helfant, H. H. Ouanabenz effects on blood pressure and noninvasive parameters of cardiac performance in patients ith hypertension. Clin. Pharmacol. Ther 19 732, 1976.

31. Sjoerdsma, A., Vendsalu, A. & Engelman, K., Studies on the metabolism and mechanism of action of metyldopa. Circulation 28. 492, 1963

32. Stjärne, L. Mechanisms of catecholamine secretion. In: Frontiers in catecholamine research. Ed. Usdin, E. & Snyder S. S. Pergamon Press, New York 1973.

33. Symposium: Labetalol. Br J Clin. Pharmacol. 3 suppl. 3. 677 1976.

34. Trolin, G G.: Involvement of α-adrenergic receptors at different levels of the central nervous system in the regulation of blood pressure and heart frequency Acta physiol. scand. suppl. 430, 1975.

35. van Zwieten, P A.. Antihypertensive drugs with a central action. Progr Pharmacol. 1 1 1975

β receptor blockers. In. Pathophysiology and management of arterial hypertension. Ed Berglund G Hansson, L. & Werkö L. A. Lindgren & Söner AB Mölndal, Sweden 1975

2. Ablad B Ek, L. Johansson, B. & Waldeck, B.. Inhibitory effect of propranolol on the vasoconstrictor response to sympathetic nerve stimulation. J Pharm. Pharmac. 22. 627 1970.

3 Adler-Graschinsky E. & Langer S Z.. Possible role of a β-adrenoceptor in the regulation of noradrenaline release by nerve stumulation through a positive feed-back mechanism. Br J Pharmacol. 53 43 1975

4 Andén, N E. & Strömbom, U Stimulation of central adrenergic alpha-receptors by L-dopa, α-methyldopa and clonidine In Central action of drugs in blood pressure regulation. Ed. Davies, D S. & Reid, J L. Pitman Medical Publishing Co. Ltd. Tunbridge Wells, Kent 1975

5 Andén, N E. Carlsson A. & Häggendal, J Adrenergic mechanisms. Ann. Rev Pharmacol. 9· 119 1969

6. Andén, N E. Corrodi, H. Fuxe K Hökfelt, B., Hökfelt, T Rydin T & Svensson T Evidence for a central noradrenaline receptor stimulation by clonidine. Life Sci. 9· 513 1970.

7 Andersson, O & Berglund G Antihypertensive effect of β 1-receptor blockade and β-2-receptor stimulation in essential hypertension. Acta med. Scand. 197 495 1975

8 Aoki K. Yoshida, T Kato S., Tazumi, K., Sato I Takikawa, K. & Hotta, K. Hypotensive action and increased plasma renin activity by Ca^{++} antagonist (Nifedipine) in hypertensive patients. Jap Heart J 17 479 1976.

9 Bock, K. D Merquet, P Brandt, T & Murata, T Experimental studies with clonidine hydrochloride in normotensive and hypertensive subjects. In. Catapres in hypertension. Ed. Conolly M. E., Butterworths, London 1970.

10 Brittinger W D Schwarzbeck, A. Wittenmeier K. W., Twittenhoff W D Stegaru, B Huber W Ewald R. W v Henning, G E. Fabricius M. & Strauch, M.. Klinisch-experimentelle Untersuchungen über die blutdrucksenkende Wirkung von Verapamil. Dtsch. med. Wschr 96. 187 1970.

11 Carlsson, A. & Lindqvist, M. Effect of chlorpromazine or haloperidol on formation of 3-methoxy tyramine and normetanephrine in mouse brain Acta pharmacol. toxicol. 20· 140 1963

12 Carlsson A. Kehr W Lindqvist M. Magnusson, T & Atack, C. V Regulation of monoamine metabolism in the central nervous system. Pharmacol. Rev 24 371 1972.

13 Day M. D & Roach, A G Central adrenoreceptors and the control of arterial blood pressure. Clin. Exp. Pharmac. Physiol. 1 347 1974

14 Doba, N & Reis, D J Role of central and peripheral adrenergic mechanisms in neurogenic hypertension produced by brain stem lesions in the rat. Circulation Res. 34 293 1974

15 Dollery C. T & Bulpitt, C. I Alpha-methyldopa. In. Central action of drugs in blood pressure regulation. Ed. Davies, D S. & Reid, J. L Pitman Medical Publishing Co. Ltd., Tunbridge Wells, Kent 1975.

16. Esler M. D & Nestel, P J Evaluation of practolol in hypertension. Effects on sympathetic nervous system and renin responsiveness. Br, Heart J 35 469 1973

17 Fleckenstein, A. Döring H. J Janke, J. & Byon K. Y.. Basic actions of ions and drugs on myocardial high-energy phosphate metabolism and contractility Hdb. exp. Pharmak. 16. 345 1975.

18 Graham, R. M., Thornell, I. R., Gain, J M., Bagnoll, C., Oates, H. F & Stokes. G. S.. Prazosin: the first dose phenomenon. Br Med. J 2: 1293, 1976

19 Henning, M.. Studies on the mode of action of α-methyldopa. Acta physiol. scand. suppl. 322, 1969

20. Henning, M.. Receptor regulation studies: significance of central catecholamine receptors in cardiovascular control. In Frontiers in catecholamine research. Ed. Usdin, E. & Snyder S. S. Pergamon Press, New York 1973

21 Henning, M.. Central sympathetic transmitters and hypertension. Clin. Sci. Mol. Med. 48. 195s, 1975

22. Henning M & Rubenson, A. Central hypotensive effect of L-3 4-dihydroxyphenylalanine in the rat. J Pharm. Pharmacol. 22. 553 1970.

23 Jäätelä A Comparison of BS 100—141 and Clonidine as Antihypertensive Agents. Eur J Clin Pharmacol. 10: 73 1976.

24 Kobinger W & Walland A.. Facilitation of vagal reflex bradycardia by an action of clonidine on central α-receptors. Eur J Pharmacol. 19· 210. 1972.

25 Lewis, P J & Haeusler G Central nervous effects of β-blockers in hypertension. In. Pathophysiology and management of arterial hypertension. Ed. Berglund G Hansson, L. & Werkö, L. A. Lindgren & Söner AB Mölndal, Sweden 1975.

26. Lidbrink, P The effect of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Brain Res. 74 19 1974

27 Ljung, B Ablad B Dahlöf C. Henning, M. & Hultberg, E. Impaired vasoconstrictor nerve function in spontaneously hypertensive rats after long-term treatment with propranolol and metoprolol. Blood Vessels 12. 311 1975

28. Muscholl, E. Regulation of catecholamine release. The muscarinic inhibitory mechanism. In Frontiers in catecholamine research. Ed. Usdin, E. & Snyder S S. Pergamon Press, New York 1973.

29 Sannerstedt, R. Haemodynamic effects of adrenergic β-receptor blocking agents in arterial hypertension. In. Pathophysiology and management

of arterial hypertension. Ed. Berglund, G. Hansson, L. & Werkö, L. A Lindgren & Söner AB, Mölndal, Sweden 1975.

30. Shah, R. S., Walker, B. R., Vanov, S. K. & Helfant, H. H. Guanabenz effects on blood pressure and noninvasive parameters of cardiac performance in patients with hypertension. Clin. Pharmacol. Ther. 19: 732, 1976.

31. Sjoerdsma, A., Vendsalu, A. & Engelman, K. Studies on the metabolism and mechanism of action of methyldopa. Circulation 28: 492, 1963.

32. Stjärne, L. Mechanisms of catecholamine secretion. In: Frontiers in catecholamine research. Ed. Usdin, E. & Snyder, S. S. Pergamon Press, New York 1973.

33. Symposium: Labetalol. Br. J. Clin. Pharmacol. 3 suppl. 3: 677, 1976.

34. Trolin, G. G. Involvement of α-adrenergic receptors at different levels of the central nervous system in the regulation of blood pressure and heart frequency. Acta physiol. scand. suppl. 430, 1975.

35. van Zwieten, P. A. Antihypertensive drugs with a central action. Progr. Pharmacol. 1: 1, 1975.

Dopamine Receptor Stimulants in Hypertension

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Until comparatively recently interest in dopamine was based largely on its position as the metabolic precursor of noradrenaline. Carlsson's (3) finding that the corpus striatum, which contains practically no noradrenaline, is extremely rich in dopamine, suggested that dopamine might have a transmitter function of its own in the central nervous system. There is now considerable evidence that this is so

Dopamine is also found in the adrenal medulla, lung, liver gut, kidney and carotid body (2, 6, 8, 14 16). Although its physiological significance in these tissues is not yet clear the fact that the amounts found vary from one tissue to another and sometimes exceed the levels of noradrenaline, suggests that dopamine may have a transmitter function in the periphery also

Dopamine has a number of pharmacological actions which differ from those of noradrenaline and which are clearly unrelated to its role in noradrenaline synthesis (for review see reference 7). Dopamine is a potent cardiac stimulant. Although this action is mediated by activation of β-adrenoceptors, increases in myocardial contractile force can be obtained at low doses without a simultaneous increase in heart rate. Heart rate is increased only at relatively high doses. This is in contrast to the β-adrenoceptor stimulant, isoprenaline, which induces parallel increases in contractile force and heart rate (Table 1) Dopamine also stimulates vascular α adrenoceptors, resulting in increases in blood pressure. After blockade of this effect with an α-adrenoceptor antagonist, a depressor effect is unmasked which is only partially inhibited by β-adrenoceptor blocking agents. The residual fall in blood pressure has been shown to be due principally to dilation of mesenteric and renal vessels. It is unaffected by ganglion blocking

Table 1. Effects of catecholamines on the heart and blood vessels in dogs and man. ↑ = increase, ↓ = decrease ↔ = no change.

		[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			
	[illegible]	[illegible] (+)	[illegible] ++	[illegible]
	[illegible]	[illegible] +++	[illegible]	[illegible]
	[illegible]			
	[illegible]	[illegible] [illegible]	[illegible] [illegible]	[illegible] [illegible]
	[illegible]	[illegible] [illegible]	[illegible] [illegible]	[illegible] [illegible]
	[illegible]	[illegible] [illegible]	[illegible] +++ [illegible]	[illegible] [illegible]
[illegible]	[illegible]	↑↑	↑↑↑	↓
	[illegible]	↔	↑↑↑	↓
	[illegible]	↓	↓↓↓	↑
	[illegible]	↑↑	↔↓	↓↓

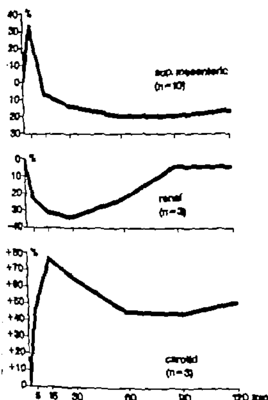


Fig. 3 Mean percentage changes in vascular resistance induced by intravenous administration of Sandoz 27 403 10 μg/kg. in the anaesthetised dog (chloralose urethane).

vessels. This probably resulted from the abrupt *fall* in perfusion pressure and consequent reduction in blood flow which occurred during the first few seconds following injection of the compound. Thereafter resistance was decreased for a period of at least two hours. A greater reduction in resistance occurred in the renal vessels. The relatively rapid recovery probably reflected intrarenal autoregulation. In contrast to these effects, resistance increased in vessels in the region supplied by the common carotid artery. The effects observed in the femoral vessels were variable. Decreases in flow in the carotid vascular bed may have been due to redistribution of blood into the mesenteric and renal vessels or to reflex constriction occurring in vessels in which dopamine receptors are not present. Direct stimulation of α-adrenoceptors by the drug can be ruled out, the compound does not increase blood pressure in spinal animals, neither does it increase tone in isolated arterial strips.

The decreases in blood pressure and resistance evoked by Sandoz 27-403 are not diminished by the *β-adrenoceptor* blocking drug, pindolol, but are abolished by pretreating dogs with the dopamine receptor blocking drugs, haloperidol (20) and ergometrine (1).

It has been shown that ligation of the renal, coeliac, superior and *inferior mesenteric arteries* abolishes the blood pressure lowering effect of dopamine (5). It was this finding that led to the conclusion that dopamine receptors are present mainly in the vascular beds supplied by these major arteries. *Sandoz 27-403* and dopamine failed to lower blood pressure after ligation of the major vessels in the abdomen. This confirmed Eble's (5) findings and also added weight to the concept that the blood pressure lowering effect of Sandoz 27-403 is due *entirely to stimulation* of dopamine receptors.

We have performed a series of similar experiments with the ergot alkaloid, bromocriptine (2 bromo-α-ergokryptine-mesylate). There is considerable evidence *suggesting* that this *drug* stimulates dopamine receptors within the central nervous system (4 11 12). Postural falls in systolic blood pressure have been reported in normotensive patients undergoing therapy with high doses of bromocriptine (9 17 18) and there are indications that the drug may lower blood pressure in hypertensive patients (13) and increase sodium excretion (unpublished observations). It seemed reasonable to assume that these effects occur as a result of stimulation of peripheral dopamine receptors.

Volkman and Goldberg (19) examined this possibility but were unable to demonstrate a dilator effect in renal vessels following close-arterial injections of doses of bromocriptine one thousand times the minimal effective dose of dopamine. We have confirmed the lack of effect following bolus intra-arterial and intravenous *injections. However* if the drug is administered slowly by the intravenous route, falls in blood pressure can be obtained from a dose of only 6 μg/kg (Figure 4). It will be noted that almost one hour is required before the maximum effect is achieved, in contrast to Sandoz 27-403 which exerts its maximum effect within 5 min of administration. The reduc-

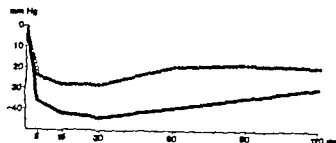


Fig 1 Effect of intravenous administration of Sandoz 27-403 on mean systemic blood pressure in the anaesthetised dog (chloralose-urethane). Mean reductions in pressure obtained in response to 2.5 μg/kg oooo (n=3) and 10 μg/kg ▬ (n=11).



Fig 2 Effect of intravenous administration of Sandoz 27-403 on heart rate in the anaesthetised dog (chloralose-urethane). Mean changes in rate obtained in response to 2.5 μg/kg oooo (n=3) and 10 μg/kg ▬ (n=11). Same animals as in figure 1

agents, atropine, antihistamines and pretreatment with reserpine, but can be selectively attenuated by the dopamine receptor blocking agent, haloperidol (20)

The extensive work of Goldberg and his colleagues has led to the concept that the action of dopamine on renal and splanchnic vessels is due *to stimulation of receptors which are specific for* the amine They have shown, in addition, that dopamine not only increases total renal blood flow but changes the cortical medullary perfusion ratio, increases glomerular filtration rate and enhances sodium excretion. It is its action on the kidney which distinguishes it from other catecholamines. The unique profile of activity of dopamine on the cardiovascular system and on renal function has led to clinical trials of dopamine for the treatment of shock, congestive heart failure, oliguric renal failure, drug intoxication and hypertension (7)

In a study performed in patients with severe hypertension (15) infusions of dopamine 1—1.5 μg/kg/min raised mean blood pressure by 10 mmHg After administration of the α-adrenoceptor blocking drug phenoxybenzamine (1 mg/kg) the dopamine infusions decreased blood pressure by an average of 77 mmHg Cardiac output was increased by 2 6 litres/min, total peripheral resistance fell by 50 % and heart rate increased by 16 beats/min. Creatinine clearance did not diminish during the period of reduced blood pressure (15) As a result of this study Goldberg (7) suggested that a substance which selectively stimulates dopamine receptors, that is, which lacks α and β-adrenoceptor stimulant activity which possesses a long duration of action and is orally absorbed might prove to be an effective antihypertensive agent.

The dopamine derivative Sandoz 27-403 (N, N-bis [6(3 4-dihydroxyphenyl) ethylamino] hexyl] *hexamethylenediamine tetrahydrobromide)* fulfils many of these criteria It induces long-lasting stimulation of vascular dopamine receptors, it does not stimulate α adrenoceptors and has only weak affinity for β-adrenoceptors. It fails to meet the last requirement in that absorption from the gastrointestinal tract is poor

Sandoz 27-403 lowers blood pressure in normotensive, anaesthetised dogs from a dose of 2.5 μg/kg given intravenously The effect is reproducible from one animal to another and lasts for a minimum of two hours (Figure 1) An important feature of the action of this compound is that, unlike most other antihypertensive agents which relax vascular smooth muscle, the reduction in blood pressure does not evoke reflex tachycardia. Relatively short lasting increases in heart rate occur in response to a dose of 2.5 μg/kg, but such an effect is rarely observed when a higher dose is given despite the fact that the blood pressure fall is greater On the contrary heart rate almost always decreases (Figure 2)

The blood pressure lowering effect of Sandoz 27-403 seems to be entirely due to dilation of vessels in the mesenteric and renal vascular beds. Blood flow in the superior mesenteric artery together with that in a renal, carotid or femoral artery was measured using electromagnetic flow probes. Regional vascular resistance was calculated as blood pressure divided by flow (Figure 3) Intravenous administration of 10 μg/kg resulted in a transient (apparent) increase in resistance in the mesenteric

bromocriptine in comparison to apomorphine, d-amphetamine and L-DOPA. Br J Pharmac. 56. 59, 1976.
13. Kaye, S. B., Shaw K. M., Ross, E. J. Bromocriptine and hypertension. Lancet I, 1176, 1976.
14. Lishajko, F. Release and uptake of dopamine in isolated granules from a human carotid body tumour. Acta physiol. scand. 79 533 1970.
15. McNay J L, McConnell, K. L., Meyer M. B., Goldberg, L. L. Hypotensive effect of dopamine in dogs and hypertensive patients after phenoxybenzamine J clin. Invest. 45 1045 1966.
16. Schümann, H. J. Ueber den Hydroxytyramingehalt der Organe. Arch. exp. Path. Pharmak. 236. 474, 1959
17. Teychenne, P F Calne, D. B., Leigh, P N., Greenacre, J. K., Reid, J L., Petrie, A., Bamji, A. N Idiopathic parkinsonism treated with bromocriptine. Lancet II, 473 1975
18. Thorner, M. O., Chait, A., Aitken, M., Benker G Bloom, S. R., Mortimer C. H., Sanders, P Mason, A. S., Besser G M. Bromocriptine treatment of acromegaly B Med. J 1 299 1975
19. Volkman, P H., Goldberg, L. L. Lack of correlation between inhibition of prolactin release and stimulation of dopaminergic renal vasodilation. Pharmacologist 18 130, 1976.
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Mats Henning
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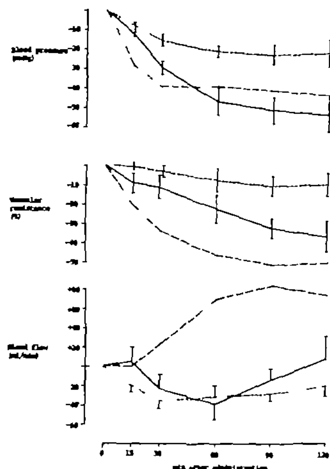


Fig 4 Effects of intravenous administration of bromocriptine in the anaesthetised dog (chloralose urethane). Mean changes (±S.E.M.) in blood pressure and resistance and blood flow in the superior mesenteric vascular bed induced by 6.25 µg/kg (n=5) ———— 12.5 µg/kg (n=5) and — — — — 25 µg/kg (n=2).

tion in blood pressure which occurred in response to 25 μg/kg was not significantly different from the response to 12.5 μg/kg. At both doses, blood pressure fell to approximately 70 mmHg. We have observed that a dopamine receptor stimulant rarely depresses blood pressure to a level below this in normotensive animals.

Resistance in the superior mesenteric (Figure 4) and renal vessels is decreased by bromocriptine, whereas that in the carotid vascular bed is unchanged or increased. The effects of bromocriptine, like those of Sandoz 27-403 are abolished by haloperidol and ergometrine confirming an effect on dopamine receptors. The hypotensive response to the drug can also be eliminated by ligating the major vessels in the abdomen. This suggests not only that the fall in blood pressure is the consequence of a vasodilator effect in the vascular beds supplied by these vessels, but also that it is a peripheral event. However there is evidence suggesting the existence of dopaminergic pathways within the central nervous system mediating hypotensive responses (10) In view of the potent stimulant effects of bromocriptine on dopamine receptors in the central nervous system, an additional action on central dopaminergic pathways concerned in blood pressure control cannot be excluded as a contributory factor in the hypotensive action of the drug.

REFERENCES

1. Bell, C., Conway E. L., Lang, W J Ergometrine and apomorphine as selective antagonists of dopamine in the canine renal vasculature. Br J Pharmac. 52. 591, 1974
2. Bertler Å., Falk, B., Hillarp N A., Rosengren, E., Torp, A Dopamine and chromaffin cells. Acta physiol. scand. 47 251, 1959
3. Carlsson, A. The occurence distribution and physiological role of catecholamines in the nervous system. Pharmac. Rev 11 490, 1959
4. Corrodi, H., Fuxe, K., Hökfelt, T Lidbrink, P Ungerstedt, U Effect of ergot drugs on central catecholamine neurons: evidence for a stimulation of central dopamine neurons. J Pharm Pharmac. 25 409 1973
5. Eble, J N A proposed mechanism for the depressor effect of dopamine in the anesthetised dog J Pharmacol. exp. Ther 145 64 1964
6. Euler U S. von, Lishajko F Dopamine in mammalian lung and spleen. Acta physiol pharmacol. néerl. 6. 295 1957
7. Goldberg, L. I Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmac. Rev 24 1 1972.
8. Goodall, McC. Studies of adrenaline and noradrenaline in mammalian heart and suprarenals Acta physiol. scand. 4 Suppl 85 1951
9. Greenacre, J K., Teychenne P F Petrie, A., Calne, D B Leigh, P N Reid, J L The cardiovascular effects of bromocriptine in parkinsonism. Br J clin. Pharmacol 3 571 1976
10. Hesse, A. Hypotensive action by central α-adrenergic and dopaminergic receptor stimulation. In. New antihypertensive drugs. E A. Scriabine C. S. Sweet (Eds) Spectrum Publications Inc New York 1976.
11. Hokfelt, T Fuxe, K On the morphology and the neuroendocrine role of the hypothalamic catecholamine neurons. In Brain Endocrine Interaction. K. M. Knigge, D E. Scott, A. Weindl (Eds.) p 181—223 S. Karger Basle 1972
12. Johnson A. M Loew D M Vigouret J M Central dopaminergic stimulant properties of

bromocriptine in comparison to apomorphine, d-amphetamine and L-DOPA. Br J Pharmac. 56: 59, 1976.
13. Kaye, S. B., Shaw K. M., Ross, E. J Bromocriptine and hypertension. Lancet I, 1176, 1976.
14. Lishajko, F Release and uptake of dopamine in isolated granules from a human carotid body tumour. Acta physiol. scand. 79: 533, 1970.
15. McNay J L., McCannell, K. L., Meyer M. B., Goldberg, L. L. Hypotensive effect of dopamine in dogs and hypertensive patients after phenoxybenzamine. J clin Invest. 45 1045 1966.
16 Schümann, H. J Ueber den Hydroxytyramingehalt der Organe. Arch. exp. Path. Pharmak, 236: 474, 1959
17 Teychenne, P F Calne, D B Leigh, P N Greenacre, J K., Reid, J L., Petrie, A., Bamji, A. N Idiopathic parkinsonism treated with bromocriptine. Lancet III, 473 1975
18. Thorner, M. O Chait, A., Aitken, M., Benker G., Bloom, S. R., Mortimer C H., Sanders, P Mason, A. S Besser Q M.. Bromocriptine treatment of acromegaly Br Med. J 1 299 1975
19 Vollman, P H., Goldberg, L. L. Lack of correlation between inhibition of prolactin release and stimulation of dopaminergic renal vasodilation Pharmacologist 18: 130, 1976.
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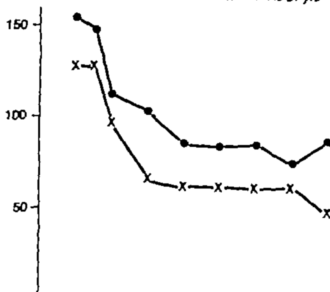
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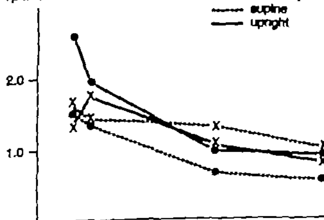
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Mats Henning
From our experiences, in acute experiments, we would expect an increase. But here I understand it was chronic treatment.

Bernt Hökfelt
With reference to the very interesting studies presented by Miss Clark concerning the hypotensive effect of dopamine analogues, I would like to present a slide showing some recent results obtained in our department. During treatment of 9 acromegalic patients, Dr Anders Nilsson has followed catecholamines in plasma and urine before and during increasing doses of the dopamine agonist brom-alfa-ergocryptine (CB 154 an ergot derivative). So far determinations have been completed only with respect to two of the patients. The figures demonstrate a marked decrease in the noradrenaline levels in plasma and urine. These figures might be of interest in view of the recently reported hypotensive effect of brom-alfa-ergocryptine.







Barbara Clark
I think this is of particular interest since it implies that there is a reduction in sympathetic tone. Experiments have been performed by Dr Scholtysik in our laboratories in which he injected bromocriptine into the cerebral ventricles in cats. He has shown a reduction in blood pressure and heart rate at a dose which is ineffective when given intravenously. It seems that bromocriptine may well have a dual action peripheral and on the central nervous system.

The Prevention of Hypertension

Gösta Tibblin and Carl-Gunnar Eriksson

From the Department of Social Medicine University of Umeå Umeå, Sweden

Abstract. Our way to prevention is to find a list of traits known to be predictors of elevated blood pressure. This list of predictors offers means for the early identification of susceptible persons. Years of experience in preventive work indicate that such identification is always useful for developing preventive programmes, since it gives a focus for action (5).

Most of the predictors show possible ways in which action could be directed towards prevention of hypertension and reduction of elevated blood pressure.

We will focus on salt, control of obesity physical exercise, and meditation. We would like to discuss preventive aspects of hypertension and the possibility of treating with other methods than drugs.

In the United States there is a development of an effective national programme to identify evaluate, and treat 20 million or more hypertensive persons (1—3) The same procedure is going on in Sweden in order to take care of our quarter of a million hypertensive persons

These national programmes are certainly a huge and complex task, requiring a great deal of care ful hard work. But, as Jerry Stamler pointed out "that challenge should not blind us to a basic fact in the long run, the ultimate solution of the hypertension problem is primary prevention, not case finding and drug treatment, important as they are now (4).

An extensive range of epidemiological studies have searched for predictors of elevated blood pressure (6—14)

The list of predictors as you see in Table 1 is sizable.

Positive family history First-born child
• Overweight—weight gain
• Glucose intolerance
• High sodium intake
• Social stress Rapid heart rate Peptic ulcer Renal disorders Hearing loss

Table 1 Predictors of hypertension.

SALT

The importance of salt in the pathogenesis of hypertension was emphasized as early as 1904 by Ambard and Beaujard, Goyton (15) indicated the overriding importance of the relationship between blood pressure and renal functional capacity to handle excess sodium in determining the presence or abscence of hypertension. The crucial role of extracellular fluid volume in the reduction of blood pressure with diet therapy and diuretics has been emphasized by many authors (16).

It is a striking fact that hypertension is not found in many less civilized populations nor does the blood pressure rise with age in these populations (13 14 16) Obviously there must be some environmental factor which accounts for the difference. From our point of view this is of great interest. Hypertension is preventible in some places! In the April issue 1976 of Circulation, Ed F ch, in an article titled Salt, volume and the prevention of hypertension (16), has summarized the literature about blood pressure in populations from widely different parts of the world including New Guinea, Malaysia, Eastern Island, Amazon

Basin, San Blas Islands of Panama, rural Uganda and the Kalahari Desert of Africa.

In every epidemiological study of this type, when salt is not added to the diet hypertension is low or absent, and when salt is used the prevalence of hypertension is high.

When we move towards the studies of western populations—Dawber in Framingham (17) and Miall in England (18) we will not find any correlation between sodium intake and blood pressure. The ordinary western diet is about 5 to 15 grams of salt per day

But if the daily intake of salt averages about 25 grams per day as in the northeastern district of Japan the prevalence of hypertension in the fifth decade would be found to be 30 to 40%

We have summarized the findings from epidemiological studies of the relationship between blood pressure and salt surveyed in Freis article in a table showing critical levels of sodium intake and the processes of developing hypertension (Table 2).

RELATIONSHIP BETWEEN DIETARY SODIUM EXTRACELLULAR FLUID (ECF) AND BLOOD PRESSURE

Salt ingested in the diet is distributed predominantly to the extracellular space. Excess amounts of salt and water are eliminated primarily through the kidneys. Guyton has linked ECF and blood pressure in the following way

The common dominator in the development of any chronic elevation of blood pressure is the need for the excretion, that is to prevent chronically expanded ECF The level of blood pressure required to produce the diuresis will depend upon the ability of a particular kidney to excrete an excess of sodium which varies from one individual to another The importance of dietary sodium in the maintenance of the ECF has been known for many years. Using Kempener rice diet, (19) which is very low in sodium (8 mEq) the ECF fell 12 per cent, there was a fall in blood pressure.

The inference from these considerations with respect to the prevention of hypertension would now seem fairly obvious. The level of ECF which we call normal is probably an expanded one compared to that of our primitive forebears. This condition has arisen because civilised man has developed his diet and a return to natural, unsalted foods will by contracting ECF reduce the stimulus to develop hypertension that presently exists in our society

OBESITY

Extensive evidence (11) demonstrates that over weight in youth, young adulthood and middle age and gains in weight in the years from young adulthood into middle age are associated with an increased risk of hypertension (Table 3). However high blood pressure does not develop in every obese person nor in every weight gainer Almost certainly factors other than simple overeating are

Table 2. Critical levels of sodium intake related to prevalence of hypertension from epidemiological studies.

Sodium per day	Prevalence of hypertension
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>350 mEg	30% of adults hypertensives

Table 3 Relationships between relative weight slope of weight curve over 20 years and prevalence of hypertension.

Relative body weight	Prevalence of hypertension
<100	128
100—112	229
113—	368
Weight slope 20 years	*Development of hypertensives*
Negative weight slope 0.4	114
Weight slope 0.5 1.4	178
Weight slope 1.5 or>	500

at work. Chiang et al. (21) in an extensive review of the literature examined 19 experimental and clinical observations on the effect of weight reduction. They found a general trend toward reduction of blood pressure. They conclude by saying that weight reduction lowers blood pressure in a considerable proportion of obese persons.

The mechanism behind the frequent coexistence of overweight and hypertension is little known.

Many obese persons have increased cardiac output. Alexander (22) postulated that an increased stroke volume is required to pump blood through an expanded vascular bed in the obese person. It is possible that the increased cardiac output influences the autoregulation of the resistance vessels so that the peripheral fluid volume is also increased in obese persons and this mechanism may therefore be working in obesity as well as in high salt intake.

PHYSICAL ACTIVITY

The trait which can be linked with low physical activity is rapid heart rate. There is no clear evidence showing that low physical activity per se is a risk factor for developing hypertension.

Physical training generally tends to decrease the resting heart rate with a decreased or unchanged cardiac output (23, 24).

Small and insignificant effects of physical training on blood pressure have been observed in young subjects (25, 26) but significant reductions in blood pressure by physical training have been obtained with sedentary 40 years old men (27) and normal older men (28). Studies on effects of physical training in hypertension are few. One study (29) of four hypertensive subjects on a four week conditioning programme showed a decrease in arterial peripheral resistance but no reduction of blood pressure. Four other studies obtained reductions in resting blood pressure (30—33). Boyer and Kasch (30) observed significant reductions in diastolic pressure (12 mm Hg) and systolic pressure (13.5 mm Hg) in 32 essential hypertensives while there was a drop only in diastolic pressure (6 mm Hg) in 22 normotensive middle-aged men after a controlled exercise programme for six months. Sannerstedt and collaborators (32) reported normalization of blood pressure after 6 weeks of physical conditioning in five subjects with latent hypertension of the hyperkinetic type. Reductions of systolic and diastolic blood pressure at rest and during submaximal work following a six-month conditioning programme have been reported by Choquette and Ferguson (33) in both normotensive and borderline hypertensive men.

The drop in pressure suggested that borderline hypertensives may derive an even greater benefit from such a programme.

PRACTICED MEDITATION

Practiced meditation is an approach which influences such predictors as "spikes" of high blood pressure, rapid heart rate and social stress.

Several studies have during the last years shown significant reduction of blood pressure using meditational techniques both in established hypertension and borderline hypertension (34—43).

The technique developed by Beary et al. (44) involves four components: a mental device, a passive attitude, decreased muscle tonus and regular practice. There is a constant stimulus of a silently repeated secret sound or word, called a mantra. The purpose of this repetition is to shift one's attention from logical, externally oriented thought. The person should sit in a comfortable position so that minimal muscular work is required and he is instructed to practice the technique for two daily 20-minutes periods, usually before breakfast and before dinner.

The meditational technique is associated with several physiological changes which are easily reproduced (45—47).

The response is believed to be associated with decreased sympathetic nervous system activity and is hypothesized to be the counterpart of Cannons emergency reaction, popularly called the fight or flight response. The decreased sympathetic nervous system activity may also carry over into nonmeditational periods during the day and result as we have heard in the decreased blood pressures noted in these investigations mentioned.

SUMMARY

The four approaches which are rational in terms of our present knowledge in order to prevent hypertension are:

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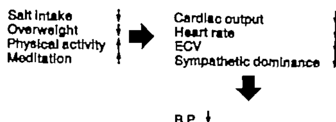


Fig 1 Measures and mechanism in primary prevention of hypertension.

3 Regular frequent exercise to achieve preliminary cardiac fitness, with consequent slowing of heart rate and parasympathetic "dominance"

No proof is available that these measures achieve the primary prevention of hypertension but they are reasonable inferences from available data.

A controlled trial among overweight persons with family history of hypertension and rapid heart rate is certainly worthwhile doing.

The recommended measures are all safe and carry considerable side-benefits in increased well being and increased fitness.

The whole programme can in a controlled trial also be recommended for application to mild hypertensives and borderline hypertension. Such a study is in the planning stage in Umeå Sweden.

Lester Breslow has formulated. It s what you do hour by hour day by day that largely determines the state of your health, whether you get sick, what you get sick with and perhaps when you die. This programme influences our way of living and gives the subject full responsibility for his treatment.

Finally I have translated my speech into the symbols used in this seminar in order to increase the understanding of my thesis and summarize my presentation (Figure 1)

REFERENCES

1 Hypertension study group Guidelines for detection, diagnosis and management of hypertensive populations. Circulation 44 A 263–A 272, 1971

2 Borhani N O Implementation and evaluation of community hypertension programs. In P Oglesby (Ed.) Epidemiology and control of hypertension. Medical Books, Miami, Florida 1975

3 Hypertension detection and follow-up program cooperative group The hypertension detection and follow-up program. Preventive Medicine 5 207 1976.

4 Stamler J.. Hypertension—a practical approach. *Little Brown* Boston Mass. 1975

5 Blackburn H.. Coronary risk factors. How to evaluate and manage them. Eur J Cardiol. 2: 249 1975

6. Geiger H. J & Scotch, N A.. *The epidemiology* of essential hypertension. A review with special attention to psychologic and sociocultural factors. I. Biologic mechanisms and descriptive epidemiology *J Chronic. Dis. 16: 1151 1963*

7 Scotch, N A. & Geiger H. J.. The epidemiology of essential hypertension A review with special attention to psychologic and sociocultural factors. II. Psychologic and sociocultural factors in etiology J Chronic. Dis. 16. 1183 1963

8. Stamler J., Stamler R. & Pullman, T (Eds): The epidemiology of hypertension. Grune & Stratton, New York 1967

9 Henry J P & Cassel, J C Psychosocial factors in essential hypertension. Recent epidemiologic and animal experimental evidence. Am. J Epidemiol. 90 171 1969

10. Gutmann, M. C. & Benson, H. Interaction of environmental factors and systemic arterial blood *pressure: A review Medicine 59 543 1971*

11 Oglesby P (Ed): Epidemiology and control of hypertension. Symposia Specialists, Miami, Florida 1975

12. Morton W E. & Knudsen, J C Correlates of hypertension among young men. Preventive Medicine 4 258 1975

13 Eyer J.. Hypertension as a disease of modern society Int. J Health Services 5 539 1975

14 Page L. B. Epidemiologic evidence on the etiology of human hypertension and its possible prevention. Am. Heart. J 91 527 1976.

15 Guyton, A. C. Coleman T G Cowley A. W Manning R. D Jr Norman, R. A. & Ferguson, J D A systems analysis approach to understanding longrange arterial blood pressure control and hypertension. Circ. Res. 35 159 1974

16. Freis, E. D Salt volume and the prevention of hypertension. Circulation 53 589 1976.

17 Dawber T R. Kannel, W B., Kagan A. Donabedian, R. K. McNamara, P M & Pearson, G Environmental factors in hypertension. In Stamler J Stamler R. & Pullman, T.N (Eds). The *epidemiology of hypertension. Grune & Stratton.* New York 1967

18. Miall, W E. Follow-up study of arterial pressure in the population of a Welsh mining valley Br *Med. J 2. 1204 1959*

19 Kempner W Treatment of hypertensi e vascular disease with rice diet. Am J Med. 4 545 1948

20. Stamler J Lectures on preventi e cardiology *Grune & Stratton New York 1967*

21 Chiang B H. Perlman, L. V & Epstein F H Overweight and hypertension. A review Circulation 39 403 1969

22. Alexander J K *Obesity and the circulation* Modern Concepts of Cardiovascular Disease 3.. 799 1963

23 Frick, M. H Coronary implications of hemo-

dynamic changes caused by physical training. Am. J. Cardiol. 22: 417 1968.
24. Astrand, P. O. & Rodahl, K. Textbook of work physiology McGraw-Hill. New York 1970.
25. Ekblom, B., Astrand, P. O., Saltin, B., Stenberg, J. & Wallström, B. Effect of training on circulatory response to exercise. Journal of Applied Physiology 24. 518, 1968.
26. Frick, M. H., Konttinen, A. & Sarajas, H. S. S. Effects of physical training on circulation at rest and during exercise. Am. J. Cardiol. 12: 142, 1963
27. Kilbom, A., Hartley L. H., Saltin, B., Bjure, J. Grimby G. & Astrand, L. Physical training in sedentary middle-aged and older men. I. Medical evaluation. Scand. J. Clin. Lab. Invest. 24 315 1969.
28. De Vries, H. A., Physiological effects of an exercise training regimen upon men aged 52 to 88. J Gerontol. 25: 325, 1970.
29. Johnson, W. P. & Grover J. A. Hemodynamic and metabolic effects of physical training in four patients with essential hypertension. Can. Med. Assoc. J. 96: 842, 1967
30. Boyer J. L. & Kasch, F. W. Exercise therapy in hypertensive men. J. Am. Med. Assoc. 211 1668 1970.
31. Hanson, J. S. & Nedde, W. H. Preliminary observations on physical training for hypertensive males. Circulation 27 Suppl. 1, 49 1970.
32. Sannerstedt, R., Wasir H., Henning, R. & Werkö, L. Systemic haemodynamics in mild arterial hypertension before and after physical training. Clin. Sci. and Mol. Med. 45. 145S 1973.
33. Choquette G. & Ferguson, R. J. Blood pressure reduction in "borderline" hypertensives following physical training. Can. Med. Assoc. J. 108. 699 1973.
34. Patel, C. Yoga and bio-feedback in the management of hypertension. Lancet 2: 1053 1973.
35. Pickering, T. Letter: Yoga and bio-feedback in hypertension. Lancet II. 1440, 1973
Answer 1440—1441 Patel, C
36. Patel, C. Yoga and bio-feedback in the management of hypertension. J. Psychosom. Res 19 355 1975.
37. Patel, C. 12-month follow-up of Yoga and biofeedback in the management of hypertension. Lancet I. 62, 1975.
38. Benson, H. Rosner B. A. Marzetta, B. R. & Klemchuk, H. P. Decreased blood pressure in borderline hypertensive subjects who practiced meditation. J. Chron. Dis. 27: 163 1974.
39. Blackwell, B., Bloomfield, S., Gartside, P. Robinson, A., Hanenson, I. Magenheim, H., Nidich, S. & Zigler R. Transcendental meditation in hypertension. Individual response patterns. Lancet I. 223 1976
40. Frankel, B. Letter: TM and hypertension. Lancet I. 589 1976
41. Patel, C. Letter: TM and hypertension. Lancet I. 539 1976
42. Stone R. A. & DeLeo J. Psychotherapeutic control of hypertension. N. Engl. J. Med. 294 80, 1976.
43. Abboud F. M., Editorial: Relaxation, autonomic control and hypertension. N. Engl. J. Med. 294 107 1976.
44. Beary J. F. & Benson H. A simple psychophysiologic technique which elicits the hypometabolic changes of the relaxation response. Psychosom. Med. 36. 115, 1974
45. Wallace R. K., Benson, H. & Wilson, A. F. A Wakeful hypometabolic state. Am. J. Physiol. 221 795 1971
46. Wallace, R. K. & Benson H. The physiology of meditation. Sci. Am. 226: 84 1972.
47. Blackburn, H. Prevention: A challenge and a promise. Medical Opinion 4 14 1975.

DISCUSSION

Lennart Hansson
I agree with Gösta Tibblin as regards the beneficial effect of reducing salt intake on blood pressure in the population but I think one should also say a word of warning against it. The effect you can expect in the individual patients is really minimal. There are some studies done by for example Antoon Amery who managed to reduce salt intake by 50% or more from approximately 180 mmol per day to 80 mmol, and the effect on blood pressure in these hypertensive patients was in the order of 3—5 mm Hg. I think you need such a drastic reduction of salt intake, that it is not sufficient just to take away the added salt. You also need salt free bread, saltfree milk and things like that, which are available for example in Belgium.

Gösta Tibblin
I have only given a review of the literature and I think we should give this approach a chance in a controlled trial. It is not necessary to have the salt consumption we have. You can certainly live with 1/2 g salt a day but it means certainly that we must start showing an interest in this.

Bengt Scherstén
In the population, we have people with low blood pressure and high blood pressure and there are about 50% of each if you consider the median value. That would mean that if the salt intake has any meaning for hypertension, those with the lowest blood pressure should have a low intake, and those with the highest blood pressure should have a high intake. This is not the case there is no such difference in the intake of salt in our population at least in the southern part of Sweden.

Gösta Tibblin
I think this is very clear and as I mentioned, Dawber and Miall made the same finding. When you

*are eating 5—15 grams a day there is no relation*ship between salt and high blood pressure You must reduce the intake to a much lower level. Nobody has found any relationship between salt intake and blood pressure in such a high salt eating population as you are referring to

Göran Berglund

I would like to point out that decreasing weight and heart rate by diet and physical training for example would not result in a large drop of blood pressure The correlation coefficient between blood pressure and heart rate and between blood pressure and weight is only about 0.2. That means that the determination coefficient would be around 0 05 which means that only 5% of the variation in blood pressure can be explained by variation in heart rate and variation in weight. So you cannot expect very much drop in blood pressure, if you change these variables.

Gösta Tibblin

I am sure that one can expect a considerable drop in blood pressure. I refer here to a lot of studies showing significant decreases in blood pressure following, for example physical activity salt reduction meditation or reduction in overweight.

Acta Medica Scandinavica

Supplementum 607

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by S Dawids and C Boe

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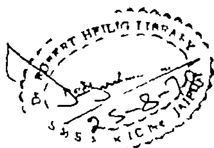
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From Medical Department P Division of Nephrology University Hospital, Rigshospitalet Copenhagen and Department of Mechanical Engineering Technical University of Denmark Lyngby Denmark

ABSTRACT The pattern of membrane support in the dialysate flow path of a dialyser is one of the most important parameters for high utilization of the membrane-area. 27 different injection moulded membrane support patterns were designed to approximate a pattern with the best overall properties. Only 15 of the patterns had acceptable properties in regard to 1) efficiency 2) compliance 3) flow resistance, 4) membrane rupture level, and 5) air retention at low flow rates. A pattern with parallel interrupted ridges perpendicular to the direction of dialysate flow showed the best overall results although differences were marginal between the best patterns. The chosen support pattern was approximately 35% better in chloride clearance at low dialysate flow and approximately 200% better at high flow than the conventional Kiil pattern.

INTRODUCTION

In the design of dialyser a number of criteria must be considered which are not only related to the performance of the item but also dictated by the available and suitable materials, their biological acceptability and their price A pleasing appearance and easiness of handling in the clinic must also be considered Although these points may heavily influence the final design, the performance is of major importance for the clinical applicability Performance depends on two important independent factors the chosen membrane and the membrane support the latter being of special importance a it determines the minute topography of the blood layer the degree of "shaded" membrane area and the submembraneous dialysate mixing.

Through the years some efforts have been made to find an efficient all round membrane support which could meet the requirements for a cheap industrial production Among available methods only the injection moulding process seems to be applicable in practice giving relative freedom of the design good tolerance of dimensions, rapid manufacturing etc Other methods can be considered and have actually been used (e.g. profile stamping punching, casting) but have proven to be too costly and complicated to handle in mass production.

Routinely used dialysers ha e mainly had three types of membrane supports. One consisting of parallel grooves as used in the Skeggs-Leonard dialyser (13) and later in the Kiil dialyser (10 14). The other consisting of multiple points, pyramids or cones as demonstrated in e.g. the Dialung (2, 3 4 7) The third is the mesh type of support initially used in coil dialysers (8 11)

Although reportedly ery efficient (primarily because of better blood geometry) a porous support made from nickel foam initially described by Babb and Grimsrud (1) proved unsuitable for routine use as the surface wa too readily compressed leaving sharp edges which in turn injured the membrane. The concept of using porous support material led to subsequent testing (9 12, 15) of other commercially available materials, but the results were generally disappointing indicating that only special purpose membrane supports could meet the requirements.

It is commonly accepted that a membrane support primarily should possess the following properties.

1) Efficient bracing of the membrane to avoid sagging especially under high transmembrane pressure gradients.

2) High utilization of the effective membrane

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For testing with organic compounds (creatinine urate) some of the test solution is continuously recirculated through the cuvette (6) of an LKB Uvicord Type 470-1A.

If one membrane support had a better efficiency for chloride compared with another support pattern, it was assumed that this would reflect a better efficiency for other substances under uniform testing conditions. To ascertain this, measurements were made with chloride, creatinine and urate on 5 support patterns.

Although the assumption proved correct, the results showed that the differences in efficiency became smaller as the membrane permeability to the substance decreased. The chloride efficiency was an easy and reproducible measurement and because of the relative high permeation factor small differences were more clearly reflected in the results. Thus only chloride efficiency results are presented for the membrane support. Each membrane support was run at least 6 times through the 24-position program, achieving 144 measurements at flow values of 50, 100, 150, 200, 250 and 300 ml/min and TMP values of 50, 100, 300 and 500 mmHg (a few support had a high resistance to dialysate flow which prevented measurement at 50 mmHg TMP because the membrane was pressed upward into the chamber and subsequently torn by the impeller). Deviation in measurements were found to be than 2% and thus the experimental error lies within approximately 8% because concentration errors are magnified in the calculations which uses differences in concentrations.

For the mathematical modelling of the system the following assumptions were made:

1) The removal of substance takes only place through the membrane area.

2) The volume of the test solution is constant during the test. (The actual loss during a run never exceeded 10–15 ml or 1% of the volume.)

3) The removal of substance from the test solution through the membrane per unit time is equal to the amount of substance leaving the dialysate compartment.

The relation between the dialysis time (T), the dialysate flow (Q) and the diffusion through the membrane is expressed by

$$T = \frac{\ln}{B} \qquad B = \frac{Q(1-\exp[-(km \cdot A)/Q])}{\text{Vol}}$$

where km is diffusion constant dependent on the diffusion through the membrane and the boundary layers and A is the membrane area. The permeation factor $P = km \cdot A$ of the equipment can be derived from this equation:

$$P = \ln\left(1 - \frac{\text{Vol} \cdot \ln 2}{Q \cdot T}\right) Q$$

As the present experimental set-up is designed to ensure that conditions above the membrane and in the membrane itself are kept constant, variations in the permeation factor (P) will solely reflect variation in the restriction to free diffusion on the dialysate side, caused by unstirred boundary layers, shading by the support pattern and by air bubbles, as well as by uneven distribution of dialysate flow. P remains uninfluenced by simple flow-dependent variations in concentration gradients and subsequent changes in mass-transfer across the membrane. Determination of P thus permits a comparison not only of the performance of different support patterns but also of the same support at different flows.

Results of measurements of T are given in man-

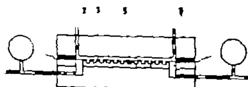


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area i e a low degree of "shading" by the membrane support largely independent of variations in transmembrane pressure gradients

3) Low dialysate flow resistance to avoid high entry blood pressure in the dialyser

4) *Continuous mixing of fluids* to reduce the phenomenon of unstirred layers

5) High resistance to membrane rupture thereby avoiding clinical "haematuria" during dialysis also with a fragile membrane

6) Low retention of air bubbles within the support pattern

These properties are however partially conflicting and consequently the resulting membrane support will always represent a compromise between merits

In practice it is thus not possible to design the ideal membrane support through calculations mainly because of the multifactorial considerations indicated above The present paper reports on experimental results on different membrane support patterns one of which is applied in a new parallel plate dialyser (5)

MATERIALS AND METHODS

Pattern construction

Evaluation of a membrane support must be performed on areas comparable at least to a single plate of a future dialyser to check flow distribution air bubble trapping flow resistance etc Areas of such sizes are not only costly but also time consuming to produce To overcome this problem an experimental injection mould was constructed to hold a 30×30 mm replaceable square matrix with any given support pattern Multiple squares were then made from each matrix and carefully glued together to form a suitable area Each new membrane support pattern could thus be made within a short time

All support patterns were tested with the same batch of Cuprophan® 150 PM (from Enka Glanzstoff Wuppertal) which was the thinnest commercially available dialysis membrane at the time

Efficiency testing

Determination of efficiency was performed by measuring the time necessary to dialyse the salinity of a given volume of test solution from one preset concentration to another (in this case half the initial concentration) against "dialysate consisting of tapwater heated to 38°C A shorter dialysis time corresponds to a higher efficiency With a known volume of test solution which is recirculated dialysed against single pass dialysate flow the relation between clearance and dialysis time can be expressed by the equation

$$CL = \frac{Vol \ \ln (C_o/C_t)}{T}$$

where CL is the clearance (in ml/min) Vol is the volume of the test solution (in ml) C_o is the initial concentration C_t is the terminal concentration, and T is the time in minutes

Efficiency was measured on a test bench which is shown schematically in Fig 1 It consists of a cylindrical chamber (12) with a volume of test solution of 1300 ml which is thoroughly mixed by an impeller (11) turning at constant speed near the bottom of the chamber The bottom consists of the dialysing membrane (10) which rests on the membrane support (13) fitted in a base plate The *base contains entry and drain channels (7) for dialysate* and is fitted with manometers (9 14) at the dialysate connections Inside the chamber an inductive conductivity meter (1) is mounted This instrument has been described in an earlier paper (6) and has the prominent feature of being practically insensitive to air bubbles in the water and on the surface of the transducer

The measurement is made between two preset

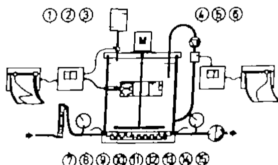


Fig 1 Diagram of test bench for efficiency testing. 1 Conductivity transducer 2, Solenoid valve remotely controlled 3 Reservoir with brine to replenish the salinity before a new run. 4 Synchronous motor 5 Small roller pump 6 Ultraviolet absorption sensor 7 Inlet of dialysate 8 Flow meter with flow regulation valve 9 Entrance pressure reading. 10 Membrane. 11 Impeller mixing the dialysate at constant speed 12, Saline volume (1200 ml) 13 Membrane support on test. 14 Exit pressure reading. 15 Effluent pressure regulation pump

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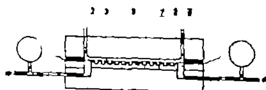


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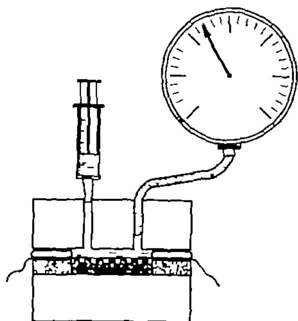


Fig 3 Schematic presentation of pressure cell for evaluation of compliance and rupture level of membrane on different membrane supports The cell is also used for casting of membrane topography

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Flow distribution and air bubble retention cou not be tested in the equipment shown in Fig 1 in the equipment illustrated in Fig 2 which ha transparent lid and a test area of 90×150 mm²

Flow distribution was evaluated both in "blood" compartment and in the dialysate partment by bolus injection of colour into the flowing liquid All patterns were tested in this w and only patterns showing uniform distributi were submitted for further evaluation of effici etc

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PYRAMID (1,2 MM)

DIALYSIS TIME T (MINUTES)

— MEASURED

--- THEORETICAL

PERMEATION FACTOR P

DIALYSATE FLOW Q (ML/MIN)

Fig 4 Graph representing the gradual improvement of performance with increasing flow For further explanation see text

Fig. 5. Graph representing sudden improvement of performance with increasing flow. For further explanation see text.

Fig. 6. Graph representing an almost constant per

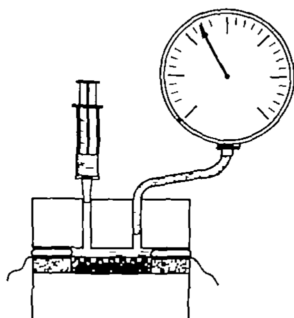


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PYRAMID (1,2 MM)
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DIALYSATE FLOW Q (ML/MIN)

Fig 4 Graph representing the gradual improvement of performance with increasing flow For further explanation see text

SEMILUNAR, COARSE

DIALYSIS TIME T (MINUTES)

PERMEATION FACTOR P (CM³/MIN)

DIALYSATE FLOW Q (ML/MIN)

— MEASURED

THEORETICAL

Fig 5 Graph representing a sudden improvement of performance with increasing flow For further explanation see text

CROSS RIDGE

DIALYSIS TIME T MINUTES

PERMEATION FACTOR P

DIALYSATE FLOW Q (ML/MIN)

— MEASURED

THEORETICAL

Fig 6 Graph representing an almost constant performance over a large flow range. For further explanation see text.

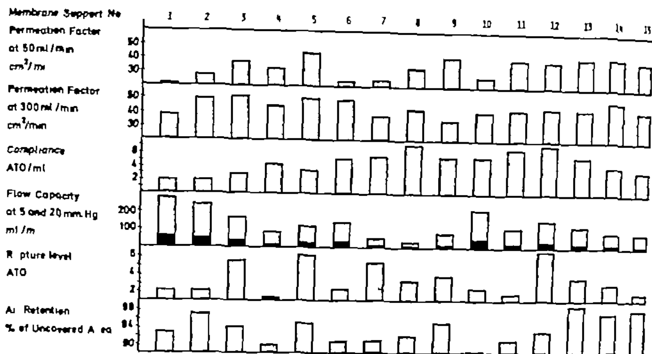


Fig 7 Diagrammatic representation of the evaluated properties of 15 membrane supports High columns indicate good performance in the particular parameter The differences between the best patterns are marginal Pattern no. 13 was chosen for support in the dialyser

any given membrane support Measurements were done when steady state conditions were present

The results are given as per cent uncovered area and presented as columns in Fig 7 Thus a high column indicates a low tendency to retain air bubbles

Flow capacity could be tested both in the equipment shown in Fig. 1 and in the equipment shown in Fig 2 The results were closely comparable Each pattern was tested twice with a constant negative transmembrane pressure at the outlet (TMP=150 mmHg) in all experiments The pressure difference (ΔP) between dialysate inlet and outlet was measured at dialysate flows of 50 100 150 200 250 and 300 ml/ min The values for each pattern are given as the flow (ml/min) at Δp of 5 and 20 mmHg and are presented as the flow capacity in Fig 7 A high column thus represents a low resistance

Membrane compliance was tested in a pressure cell shown in Fig 3 One chip of the membrane support patterns is fitted in the base of the sealing rim The cell is mounted under water to prevent air retention within the cell A manometer filled with silicone oil (to reduce the elasticity of the volume) and a syringe containing water is connected through the lid The deflexion of the membrane is determined by measuring the increase in pressure as the contents of liquid in the syringe is displaced into the cell Repeated trials with the same membrane gives different graphs because a permanent stretching of the membrane occurs A new membrane must therefore be fitted for each trial The elasticity of the system is determined in the same manner by using chips with a smooth surface made in the same way as the chips with patterns The true membrane elasticity on the tested support pattern is thus the difference between these two measurements. Six test series were carried out with the membrane oriented in two perpendicular directions in each test The membrane is anisotropic and expands approximately 10% when moistened in its longitudinal axis but only of a minor order in its transverse axis The values did not deviate much but the presented values are those with the lateral axis of the membrane parallel to the direction of the dialysate flow (as this is the way it would be oriented in the parallel-plate dialyser)

From the resulting almost linear graphs the slope is determined The values were found in every given support to vary less than ±3% and the average value is given as the pressure increase as a function of volume increase (Ato per ml) A high value presented as a high column in Fig 7 thus represents a support with stiff bracing properties

Membrane rupture value was tested in the same

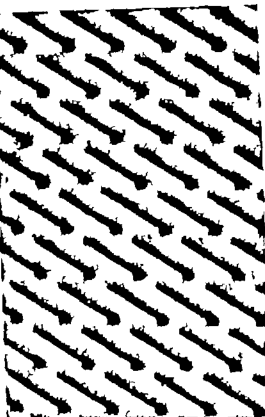


Fig. 8 A cast of the membrane resting on support no. 13 at 500 mmHg. Note the uniform settling of the membrane.

cell in connection with the compliance measurements. The rupture value was recorded as the pressure when the membrane gave in. The values did not vary more than 5% and the mean value is given in ato in Fig. 7. Thus a high value represents a support with good bracing properties.

Topography of blood layer was evaluated at TMP of approximately 400 mmHg by making cast with a suspension of dental plaster of Paris which does not shrink during setting. Each cast was studied to learn how the membrane settled on the support pattern. A poor adjustment of the membrane resulted in harp bends in the profile. We judged it important to obtain ery even blood contact surface as bends and wrinkles were considered potential sites for thrombous formation. The results are not show but they were considered during the selection of the best support.

Fig. 8 shows an example of a uniform settlement of the membrane over an area of membrane support.

RESULTS

27 different injection moulded types of membrane supports were analyzed. 1? of the supports were however found to have so faulty properties in one or more tests that they were rejected before comparative evaluation. The remaining 15 were compared as shown in Table I. This table gives in numbers the results of the tests. In Fig. 7 the values are shown as columns. A high column indicates good performance of each property. The support which combined good merits for all the tested parameters was selected for use in the dialyser to be constructed.

From the experimental results efficiency graphs for finer evaluation were computer drawn by an IBM 1130 with a Plotter 1442 for all the supports.

The least square fitted curve for the dialysis time was calculated and the resulting fitted graph for the permeation factor *P* was calculated. At the highest value of *P* the ideal graph for the theoretically best dialysis time was calculated. Figs. 4–6 give three examples of typical graphs. The graph with triangular values is *P* the graph with superimposed standard deviations is the experimental performance. The broken graph represents the "ideal" graph (with constant *P* of the support when it is best).

In Fig. 4 *P* increases as *Q* increases, indicating a progressive improvement of the dialysate mixing, probably due to a reduction of the unstirred layer phenomenon.

In Fig. 5 *P* "rises" from one level to higher level probably partly as a result of the release of airbubbles in the support pattern when *Q* increases.

In Fig. 6 *P* maintains an almost constant value throughout the whole flow range indicating a uniform all-round performance.

DISCUSSION

Although the obtained results give a firm basis for the selection of a membrane support with uniform performance within a wide range of dialysate flow values, it should be pointed out that the performance of a dialyser with the support in question cannot fully be predicted because the dimensions of the individual blood layers as well as the dialyser as a whole also has profound influence. From Table I which gives the summary of the values on the best support patterns one can see that a higher permeation factor is obtained with

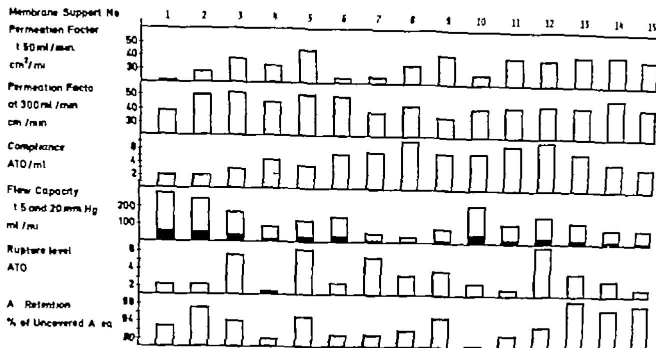


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Membrane rupture value was tested in the same

7	8	9	10	11	12	13	14	15
Z-pattern, fine	Comb-pattern	U-pattern	Cross-pattern	Cross +Tenon	Cross-ridge, fine	Cross-ridge, medium	Cross-ridge, coarse	Cross-ridge large
24.8 (5.3)	34.1 (1.3)	42.0 (3.2)	17.7 (9.9)	40.4 (4.1)	39.7 (4.7)	42.5 (0.8)	43.1 (1.6)	41.9 (5.2)
38.6 (0.7)	37.0 (2.3)	43.5 (3.5)	42.1 (2.0)	43.4 (2.2)	44.7 (1.5)	44.2 (1.7)	50.7 (2.3)	44.1 (2.6)
5.6 (0.1)	7.4 (0.1)	5.6 (0.0)	5.6 (0.1)	7.1 (0.1)	7.5 (0.1)	5.7 (0.1)	4.3 (0.1)	3.7 (0.1)
14 (1.3)	11 (1.4)	19 (1.2)	50 (1.9)	24 (1.1)	36 (1.3)	26 (1.3)	20 (1.2)	19 (1.2)
56 (1.1)	38 (1.4)	83 (1.2)	218 (1.8)	109 (1.2)	155 (1.3)	123 (1.2)	91 (1.3)	88 (1.2)
5.3 (0.0)	3.4 (0.1)	3.9 (0.0)	2.5 (0.1)	1.9 (0.1)	6.7 (0.1)	3.6 (0.1)	2.9 (0.0)	1.9 (0.1)
9	8	5	12	7	5	1	3	2

the clinician because it could result in a high extracorporeal volume at high transmembrane pressure gradients. Furthermore the sagging results in an increased shading of the membrane. By introducing a thicker and stronger membrane this tendency can be reduced but this often means an increased diffusion resistance. The membrane used in these experiments is—as earlier mentioned—anisotropic and packing the membrane (as performed in production of dialysers) in a dry condition can result in an uneven bracing when it becomes wet.

For this reason a membrane support with parallel oriented ridges braces anisotropic membranes in a more uniform fashion than a support pattern where the ridges form angles or are oriented in more than one direction. This could be shown on the casts made of the membrane topography. It is of interest to note that although a good compliance of a support is achieved this does not necessarily go for the rupture level. A low rupture level value must indicate that a localized concentrated drag is applied on the membrane and the plaster casts *indicate* that

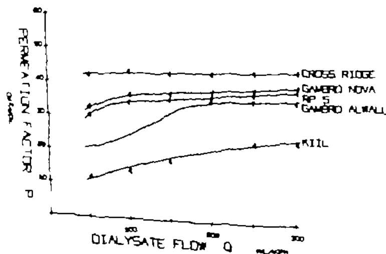


Fig. 10. The graph shows the permeation factor for patterns from 4 well known dialysers in clinical use. The graph denoted cross ridge represents support no. 13

Table I

Membrane support no			1	2	3	4	5	6
			Description of support patterns					
	Unit	*n*	Pyramid (1.2 mm)	Pyramid (0 8 mm)	Semilunar coarse	Semilunar +Teflon	Semilunar fine	Z-pattern coarse
Permeation factor at 50 ml/min	cm^2/min	24	20.5 (0 7)	28 0 (2.6)	37 8 (2.5)	33 1 (1 4)	44.5 (4.2)	23 7 (4.2)
Permeation factor at 300 ml/min	cm^2/min	24	38 5 (0 7)	50.5 (6.8)	52.2 (1 9)	45 3 (1 0)	51.3 (2.8)	30 0 (4 1)
Compliance	ATO/ml	6	2 0 (0 1)	2.0 (0 1)	[illegible]9 (0 1)	4.[illegible] (0 0)	3.5 (0 0)	5.2 (0.1)
Flow capacity at 5 mmHg	ml/min	12	62 (1 2)	55 (1.3)	39 (0.9)	21 (1.2)	27 (1 4)	33 (1 1)
Flow capacity at 20 mmHg	ml/min	12	272 (3 1)	241 (2.8)	167 (1 4)	92 (1.2)	12[illegible] (1.2)	145 (1.8)
Rupture level	ATO	6	2.1 (0 1)	2.1 (0 1)	5.5 (0 1)	1.3 (0 0)	6.1 (0 1)	2.3 (0 0)
Air retention at 50 ml/min	% of area	1	7	3	6	10	5	9

most of the supports with increasing dialysate flow This is in our opinion an important fact which has frequently been overlooked A low velocity in the dialysate will in most supports tend to formation of unstirred boundary layers and—more important—retention of air bubbles which normally are abundantly present as a result of insufficient deaeration of the dialysate Both of these disadvantages can be reduced or eliminated if recirculation of dialysate is used—a method that consumes no more dialysate In this case the flow capacity of the support pattern becomes a most important factor

Compliance is normally considered important by

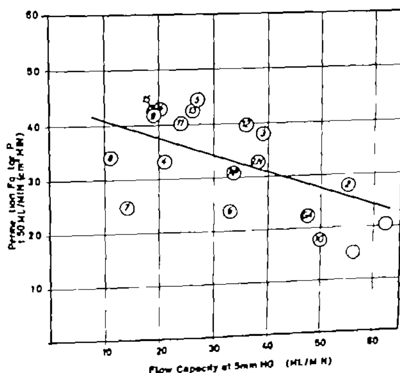


Fig 9 The permeation factor at 50 ml/min plotted against the flow capacity at 5 mmHg for the tested support patterns The figure in the circles indicate the pattern number The values of Gambro Alwall (*GA*) Gambro Lundia Nova (*LN*) Rhone Poulenc s RP 5 (*RP*) and Kiil (*K*) are inserted. The graph represents the least square-fitted graph. (P=44.3953−0.333 Q) r^2=0 3136

A New Parallel Plate Dialyser

II. *Description of Design and In Vitro Performance*

S Dawids and C. Boe

From Medical Department P Division of Nephrology University Hospital, Rigshospitalet Copenhagen and Department of Mechanical Engineering Technical University of Denmark, Lyngby Denmark

ABSTRACT Using a high efficiency membrane support pattern described in the previous paper a prototype of a new parallel plate dialyser has been developed. The new dialyser is designed in such a way that the number of components is reduced to one item per blood layer and the membrane is folded as a continuum. This permits a semiautomatic assembly of the unit, which reduces production costs. Furthermore this technique facilitates aseptic handling of the item. The in vitro performance has been tested and it compares favorably with commercially available disposable parallel plate dialysers.

INTRODUCTION

The clinical applicability of a dialyser depends primarily on its efficiency in extracting uremic waste products and removing water through ultrafiltration. However a number of other requirements are necessary before the dialyser is accepted in the clinic and these can be roughly summarized as follows.

1 Non-toxic sterilizable materials of uniform quality must be used combined with good blood compatibility

Extraction ability (i e clearance) must be good and reproducible even during high transmembrane pressure

3 Good controllable reproducible ultrafiltration

4 Low frequency of membrane rupture

5 A low blood volume and good compliance combined with low flow resistance to blood and dialysate

6 Low amount of residual blood at termination of treatment

7 Pleasing appearance and easiness of handling combined with good storage properties.

8 Low priced (indicating simple and rapid manufacturing).

As some of these points are somewhat conflicting the resulting dialyser design usually will have to emphasize a few of the above mentioned requirements at the expense of other less important virtues

Although no exact knowledge exists as to the nature of the uremic toxins the suggestion that medium range molecules may play a significant role in the uremic syndrome (2, 3 4 12, 13 22, 23 26) has spurred research on new materials for membranes (5 9 10 11 14 15 17 19 20 24) Cellophane has however so far proven superior primarily because of its uniform quality and its price. Thin types of cellophane show an increased permeability to middle molecules as compared with thicker membranes (9 14 16, 25 27). Unfortunately this advantage of the thin membrane is counterbalanced by its weaker structure resulting in a higher tendency of rupture and thus underlines the necessity of a careful and individualized design of the membrane support in the dialyser (1 6 8, 1 5 28)

GENERAL DESCRIPTION

The tested prototype (Fig. 1) contains 14 parallel blood layers each formed between simple plates inserted in pouches of the membrane

The single injection moulded plate (Fig. 2) includes the ports for blood and for dialysate as integrated parts The blood ports are folded into a spindle shaped congruent concavity on the plate allowing a very smooth transition between the surfaces of the blood port and those of the plate The formation of very fine flash lines at the transition points reduce possible leaks at this critical location to a negligible size

this is on corners points and shoulders of ridges especially if these are only slightly rounded Off hand one would expect that an efficient mixing resulted in a higher flow resistance (equal to a reduced flow capacity) A plot of permeation factors at 50 ml/min versus flow capacity shown on Fig 9 confirms this The considerable deviation from this rule may be caused by variable air bubble retention and shading in the low range of the testing conditions i e at dialysate flows of 30–100 ml/min. (*which corresponds to the flow velocity of dialysate* in clinical dialysis)

On the basis of the results shown in Table I support no 13 was chosen for the dialyser design The best supports have admittedly only marginal differences in the properties and the decision was based on the overall performance with emphasis on the clinically important parameters (efficiency compliance rupture level and air retention)

The support constructed on the basis of our tests compares favourably with support patterns of 4 commercially available dialysers (Fig 10) It should however again be emphasized that these results per se do not reflect the performance of the respective dialysers which does not only depend on the support pattern

REFERENCES

1 Babb A L. & Grimsrud L. A new concept in hemodialyzer membrane support Trans Amer Soc artif *intern. Org 10-31 1964*

2. Bluemle L. W Basic design of the dialyzer Proc. Conf on Hemodialysis. N I H Bethesda, Ma 96 1964

3 Bluemle L. W Technical aspects of dialysis New apparatus Proc. 3rd Int Congr Nephrol 3 256 1967

4 Bluemle L. W Dickson J G Mitchell J & Podolnick, M S Permeability and hydrodynamic studies on the MacNeill-Collins dialyzer using conventional and modified membrane supports. Trans Amer Soc artif intern Org 6.38 1960.

5 Dawids, S & Boe C A new parallel plate dialyser II Description and in vitro performance Acta med. Scand Suppl 607 17 1977

6. Dawids S Boe C & Andreasen, M M. A new hemodialysis console II Description of components. Acta med Scand. 193 379 1973

7 Esmond W G Strauch M Baker B Lewinna, A Aattar S Blair E. & Cowley R A Compact autoclavable countercurrent hemodialyzer with disposable components Biomed Sci Instrum 1 363 1963

8 Hoeltzenbein J A new disposable coil system Proc. Europ Dial Trans Ass. 3 390 1966.

9 Hoenich N A Jolly D & Frost T H A Test Cell for the Evaluation of Membrane support Materials and Membranes. Proc Europ Dial Trans Ass. 8 416 1971

10 Kiil F Development of a parallel flow artificial kidney in plastics Acta Chir Scand 253 143 1960.

11 Kolff W J & Watschinger B Further development of a Coil Kidney J Lab Clin Med 47 969 1956.

12 Simpson K M West G R. Blainey J D Dawson-Edwards, P & Hilton D D A hydrodynamic test cell for the investigation of dialyser design Proc Europ Dial Trans. Ass 4 107 1967

13 Skeggs L. T & Leonard J R. Studies on an artificial kidney I Preliminary results with a new type of continuous dialyser Science 108. 212, 1948

14 Takagishi J W Barbour B H & Orrell F L. Development and clinical evaluation of a high performance dialyzer N I H report Contract PH 43-66-961 Western Gear Corp. 1970

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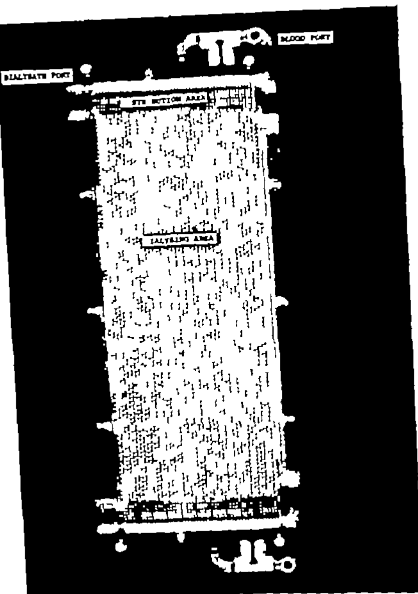


Fig 2 A single injection moulded plate Note the spindle shaped variation in thickness of the blood port and the corresponding sealing areas

factors have no injuriou influence on the dialysers efficiency They do however play a role during the wash-out of blood with sal ne at the termination of dialysis. The volume of saline required will be approximately 30 per cent greater than if the multiple flow paths were of exactly identical length.

DIALYSER IN VITRO TESTING

Prior to the regular testing it was observed that slight variation occurred in the properties of the membrane from batch to batch Similar variations are well known (14 15 16 26) and can amount to 10% in ultrafiltration rate and 5–6% in clearance Consequently each test in the subsequent series was run on dialysers built with membrane material from a chosen batch with average properties

Priming volum and compliance was measured in 6 dialysers from the same batch The blood compartment was filled with liquid while the dialyser was suspended from a balance (Sartorius type 2E) mounted with a displacement transducer (Kroijer Jensen type LDI 5050) in connection with a carrier wave bridge (K J type 5100 A) The static pressure

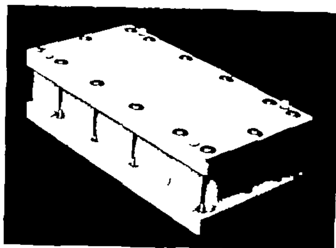


Fig 1a Prototype A of the Boe–Dawids dialyser

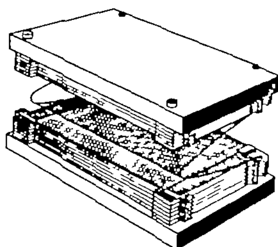


Fig 1b Diagram showing the mutual positioning of injection moulded plates blood ports and the fol membrane

As the dialyser is built the membrane is folded back and forth as a continuum every other time inserting a plate from one side into the formed pouches and subsequently folding the blood ports into the pouches opening towards the opposite side The correct mutual positioning of plates and blood ports is obtained by taps along the edges which fit into corresponding vertical holes on the next plate The vertical blood distribution channels are formed by the stacked blood ports and the dialysate distribution is in principle the same with a vertical channel formed by the dialysate ports The blood layers are sealed by sealing rims along the borders of the plates and blood ports

The principle of this design not only ensures a simplified production because only one moulding form is necessary but also ensures a good tolerance fit between the plate and the blood ports in spite of variable shrinking properties of the plastic material The design results in an effective blood-dialysate separation because the blood and dialysate enter each side of the dialysing area over a folded part of the membrane without any free edges at the entry sites If a minor leak e g at the dialysate ports should occur this can only drain to the exterior of the dialyser with no chance of entering the blood compartment Membrane leakage of fluids only occurs when there is actual rupture of or hole in the membrane

INTERNAL FLOW PATTERN

The flow pattern in the blood layer is influenced by the fact that entry and exit of the blood is located along the same side of each plate with a shallow relatively narrow blood distribution area extendi across the surface to the opposite border of t plate Blood entering the membrane area via t blood port is spread out in the blood distributi area and subsequently directed over the dialysi area The blood which flows near the edge whe the blood ports are located will enter the dialysi area immediately after it has entered the blood di tribution area and earlier than the blood whic travels varying lengths in the blood distributio area Thus the entering blood will form an oblique advancing front across the dialysing area At th exit an additional delay occurs because of the sym metry of the plate

Accordingly experiments with contrast injecte selectively as a bolus into individual blood layers o a dialyser during X-ray screening revealed an ob lique contrast front. This front moved evenly along the dialysing area indicating that flow distribution across the single blood layer was uniform

The blood layers are located at different dis tances from the dialysers blood entry and exit As a result the blood reaches the upper blood layers be fore it reaches the bottom layers and again the blood from the top layers reaches the exit relatively earlier because of the symmetry

Contrast injection revealed a slightly higher flow in the bottom layers however not of a magnitude to measurably reduce the delay discussed above

Since the velocity in the blood compartments is practically identical within layers as well as be tween layers the above mentioned design related

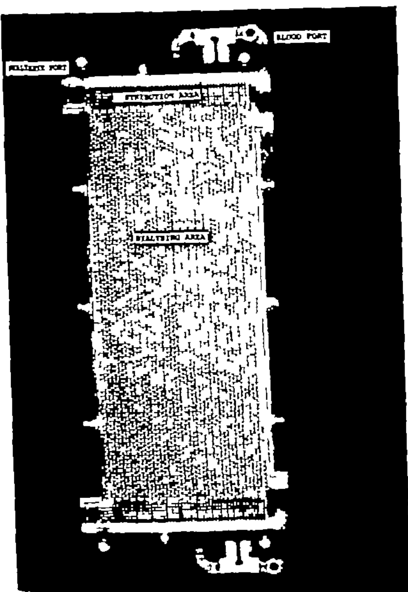


Fig 2 A single injection moulded plate. Note the spindle shaped variation in thickness of the blood ports and the corresponding sealing areas.

factors have no injurious influence on the dialysers efficiency. They do, however, play a role during the wash-out of blood with saline at the termination of dialysis. The volume of saline required will be approximately 30 per cent greater than if the multiple flow paths were of exactly identical length.

DIALYSER IN VITRO TESTING

Prior to the regular testing it was observed that slight variations occurred in the properties of the membrane from batch to batch. Similar variations are well known (14, 15, 16, 26) and can amount to 10% in ultrafiltration rate and 5–6% in clearance. Consequently each test in the subsequent series was run on dialysers built with membrane material from a chosen batch with average properties.

Priming volume and compliance was measured in 6 dialysers from the same batch. The blood compartment was filled with liquid while the dialyser was suspended from a balance (Sartorius, type 2E) mounted with a displacement transducer (Kroijer Jensen type LDI 5050) in connection with a carrier wave bridge (K J type 5100 A). The static pressure

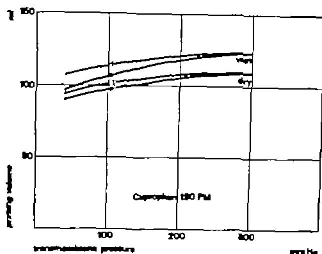


Fig 3 Priming volume as a function of transmembrane pressure in dry (silicone oilfilled) and wet (waterfilled) in the prototype. Stretching of the membrane during high TMP results in a subsequent permanent increase of volume

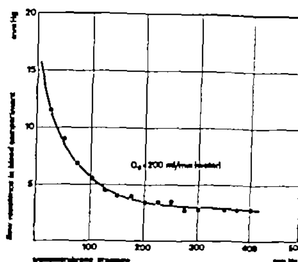


Fig 4 Flow resistance in the blood compartment at 200 ml/min as a function of transmembrane pressure

in the blood compartment was measured with an integrated transducer unit (Tyco Model AB 0–15 p s i)

A simultaneous calibrated recording of the weight (I e volume) as a function of the transmembraneous pressure was recorded on an X Y recorder (Moseley Autograf Model 7000 A R) Each test was run within 30 seconds to avoid errors from ultrafiltration The pressure was increased from 0 to 300 mmHg. The weight was measured better than 0.5 g and the transmembraneous pressure (TMP) was *measured better than 1 mmHg Tests were made on* 3 dry (silicone oil filled) and 3 wet (water filled) dialysers

The results given in Fig 3 show a priming volume of 91 ml in the dry condition and 97 ml when the membrane is wet It is seen that with increasing pressure on the membrane a stretching of the film occurs resulting in an increase of blood volume At 300 mmHg the volume is 110 ml and 124 ml in dry and wet conditions respectively When the pressure *is relieved* the shrinking is incomplete (dry 95 ml and wet 107 ml) indicating that a permanent stretching of the membrane has taken place

Flow resistance in the blood compartment—defined as the pressure difference in mmHg between entry and exit of the blood compartment—was made on 4 dialysers A water flow of 200 (±3) ml/*min* at 20°C was established with an occluding laboratory rollerpump The flow was read on a flow meter at the exit (Brook D & R 6–15 A)

The dialysate compartment was left open The transmembrane pressure defined as the mean value in the blood compartment and read with precision manometers (NAF aneroid) at entry and exit was initially set at a value of approx 25 mmHg and subsequently increased in steps of 25 mmHg up to a TMP of 400 mmHg Sixteen sequential measurements were made in the range 25–400 mmHg.

The results given in Fig 4 show that the pressure drop through the blood compartment at clinical levels of transmembrane pressure (TMP) (i.e. 100–200 mmHg) is approximately 5 mmHg at a flow in the blood compartment of 200 ml/min

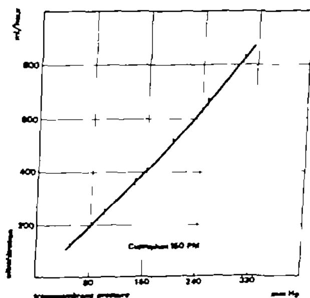


Fig 5 In vitro ultrafiltration rate (ml/hou) a a function of transmembrane pres ure

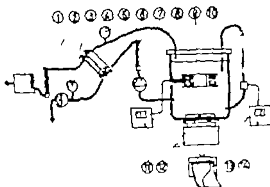


Fig 6 Schematic diagram of the testbench for clearance measurements. (1) Through-flow thermostat, (2) Dialysate flowmeter with flow regulator (3) Effluent pump (4) Manometer showing the relative dialysate pressure level, (5) Manometer showing the exit pressure in the dialyser's blood compartment, (6) Dialyser being tested (7) flowmeter showing the entry flow in the blood compartment, (8) laboratory roller pump (9) reservoir with solute, (10) small laboratory roller pump circulating solute (11) inductive conductivity sensor (12) laboratory heater with magnetic stirrer (13) recorder (14) concentration measurement of organic solutes based on ultraviolet absorption

Ultrafiltration was measured as the reduction of volume of 2 liters of saline recirculated through the blood compartment A constant dialysate flow of 600 ml/min ± 10 ml/min through the dialysate compartment was maintained throughout the testing period The transmembrane pressure was established with an effluent pump earlier described (7)

The ultrafiltered volume was recorded in 3 subsequent periods of 20 minutes at 6 TMP values (50 100, 144 199 49 and 300 mmHg) The average values shown in Fig 5 are gi en in ml/hour Variations were found to be within 6% provided dialysers used for testing were mounted with membrane material from the same batch.

The results shown in Fig. 5 show an almost linear correlation between the transmembrane pressure and ultrafiltration rate with a mean value of 252 ml/h at TMP of 100 mmHg and 821 ml/h at 300 mmHg

Membrane ruptur resistance defined as the TMP value at which the membrane in the dialyser ruptures was tested on six dialysers on a simple test bench

A water reservoir containing 0.5 liter solution of dark brown 0.1% dextran-iron complex ($M = 75000$, Jeferon ...

of the dialyser and to a valve from which water is replenished during the violent ultrafiltration at high TMP values The dialysate compartment is left open A small pneumatic oscillator exposes the blood compartment of the dialyser via the reservoir to an intermittent pressure of 5 seconds duration and a subsequent period of 5 seconds with no pressure Each dialyser was exposed to a stepwise increasing pressure every two hours until a TMP maximum of 1900 mmHg (2.5 Ato) was reached after 10 hours and exposure at this level was maintained at least for 120 hours.

The TMP levels at which rupture of the membrane occurred was not determined as none of the six tested dialysers showed any sign of membrane ruptures, detected as brown discoloration of the ultrafiltrate At even higher pressure levels the dialysers clamping system gradually gave in and caused progressi e leaking to the exterior of the dialyser

Clearanc was tested for chloride ($M = 35.5$) creatinine ($m = 113$) uric acid ($M = 168$) bromsulphaleine ($M = 838$) polyethylene glycol ($M = 1000$) and B_{12} ($M = 1355$)

The clearances were determined on a testbench shown schematically in Fig. 6 A reservoir (9) containing 5 liters of aqueous solution is stirred and thermostated to 38°C (12) w th a combined magnetic stirrer and heater (Heidolph type MK II) The solution is continuously recirculated with an adjustable laboratory roller pump (8) via a flowmeter (Brook D&R 6-15A) (7) through the blood compartment of the dialyser (6) and returned to the reservoir Tap water thermostated to 38°C in a laboratory through-flow thermostat (1), is used as dialysate and flows counter-current via another flowmeter (F&P Co 3F 3/8) (2) through the dialysate compartment A negative dialysate pressure of 90 mmHg is established with an effluent pump (3) described in an earlier paper (7) and adjusted according to readings on a precisions manometer (NAF) (4) The pressure at the outlet of the blood compartment is held constant at 130 mmHg with an overflow arrangement on the return line to the reservoir The concentration of chloride is measured with an inductive conductivity meter (11) also previously described (7) The time related chloride measurement is recorded (Servogor recorder type RE 511) (13) Organic solutes (creatinine uric acid and bromsulphaleine) are separately measured by

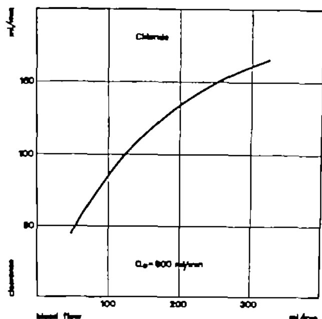


Fig 7 In vitro clearance of chlorid as a function of variable Q_B

and likewise recorded (13) The time related concentrations are subsequently derived from standard graphs An exception from this type of measurement was the B_{12} test where isotope tagged B_{12} was used The vitamin solution containing 10 μCi CO^{58} was mixed with 10 liters of water which was recirculated through the dialyser Five ml samples were drawn at each run Six tests were made at different blood flow values (50 100 150 200 250 300 ml/min) The activity was determined in a liquid scintillation counter (Hewlett Packard Armarc Model 446) with an error less than 0 5% The efficiency Cl (clearance) was calculated from the equ ation

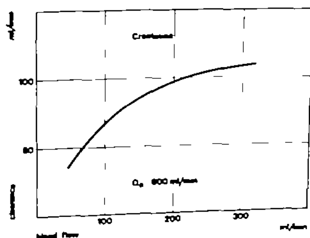


Fig 8 In vitro clearance of creatinine as a function of variable Q_B

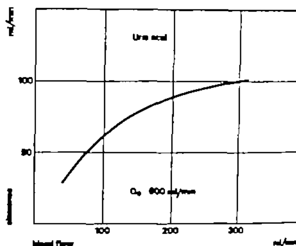


Fig 9 In vitro clearance of uric acid as a function of variable Q_B

$$Cl = \frac{Vol \ \ln (C_o/C_t)}{t} \ (ml/min)$$

where Vol is the average volume during the test C_o and C_t are concentrations initially and at the time t

The results are given in Figs 7–12 At blood flow of 200 ml/min and dialysate flow of 600 ml/min the in vitro clearance values were the following Chloride 139 ml/min creatinine 96 ml/min, uric acid 87 ml/min bromsulphaleine 37 ml/min polyethylene glycol (Carbowax® 1000) 35 ml/min B_{12} 44 ml/min

With a dialysate flow of 1000 ml/ min and unchanged blood flow the values increased as follows Chloride 141 ml/min creatinine 101 ml/min uric acid 89 ml/min bromsulphaleine 37 ml/min PEG (1000) 35 ml/min B_{12} 45 ml/min

The relation between clearance and varying dialysate flow at constant blood flow is given in Fig 13 for chloride and creatinine It is seen that an increase of dialysate flow from 600 to 1000 ml/min

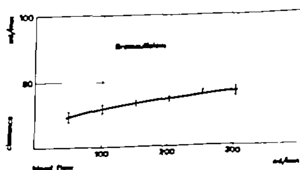


Fig 10 In vitro clearance of bromsulphalein as function of variable Q_B

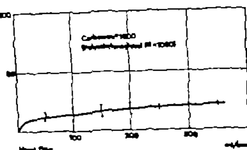


Fig 11 In vitro clearance of polyethylene glycol (M=1000) as function of variable Q_B.

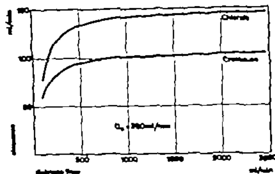


Fig 13 In vitro clearance of chloride and creatinine a function of variable dialysat flow Q_D.

only results in a moderate gain of clearance being 5% for chloride and 3% for creatinine. It should be noted that a significant increase of efficiency could not be seen when a local recirculation (2000 ml/min) w s established (not shown in figure)

DISCUSSION

The chief merit of this dialyser is considered to be the simple design which is achieved by integrating the blood and dialyser ports, sealing rims etc in the plate and by using one single length of membrane for each dialyser thereby avoiding manufacture and manipulation of separate membrane sheets for each layer The semiautomatic assembly enables a cheaper production. Furthermore it ensures larger safety against contamination since a no-touch technique can be employed which is of special importance in the handling of the membrane and the blood compartment The experimental results indicate that the clinically important virtues of a dialyser are contained in this prototype

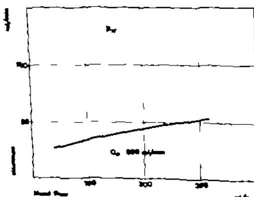


Fig 12 In vitro clearance of vitamin B as function of variable Q_B

The efficiencies (e g creatinine clearance of 96 ml/min at blood flow of 200 ml/min and dialysate flow of 600 ml/min) are very satisfactory in particular as these results are obtained with a dialysing area of only 0 94 m² An increase of area to 1 m² would increase the estimated efficiency approximately by 5–6% taking into account the resulting lower flow velocities in the individual layers.

The membrane support pattern thus seems to live up to the expectations of a relatively high efficiency at low dialysate flow elocities. The remarkably good clearance with polyethylene glycol and B_{12} indicates a good efficiency in the range of middle molecules The tests with variable dialysate flow (Fig. 13) show that dialysate flow above 550–600 ml/min in this dialyser only adds a trifle to the efficiency wherea a reduction of the dialysate flow below 500 ml/min progressively w ll reduce the ex traction.

The above mentioned underlines that a sufficient blood flow through a dialyser is the main prerequisite for a good clearance

The in vitro ultrafiltration shows modest values again because of the small dialysing membrane area in the prototype (0 94 m²) Corrected values for a membrane area of 1 m² would be approximately 310 ml/h per m² at TMP of 100 mmHg.

Table I *Technical specifications on Boe–Davids dialyser (prototype)*

Weight without clamping	1.5 kg
Weight with clamping	2 kg
Blood layers	14
Membrane area	0 94 m²

Dimensions: 33 16 11 cm.

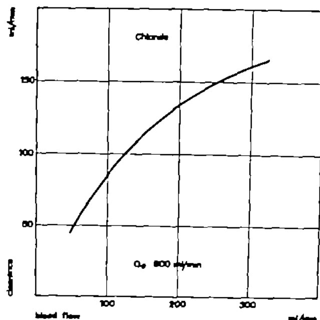


Fig 7 In vitro clearance of chlorid as a function of variable Q_B

and likewise recorded (13) The time related concentrations are subsequently derived from standard graphs An exception from this type of measurement was the B_{12} test where isotope tagged B_{12} was used The vitamin solution containing 10 μCi CO^{58} was mixed with 10 liters of water which was recirculated through the dialyser Five ml samples were drawn at each run Six tests were made at different blood flow values (50 100 150 200 250 300 ml/min) The activity was determined in a liquid scintillation counter (Hewlett Packard Armarc Model 446) with an error less than 0 5% The efficiency Cl (clearance) was calculated from the equation

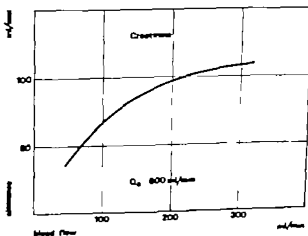


Fig 8 In vitro clearance of creatinine as a function of variable Q_B.

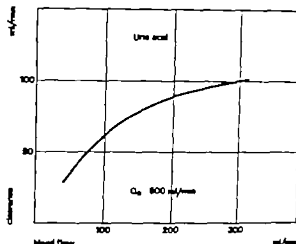


Fig 9 In vitro clearance of uric acid as a function of variable Q_B

$$Cl = \frac{Vol \ \ln (C_o/C_t)}{t} \ (ml/min)$$

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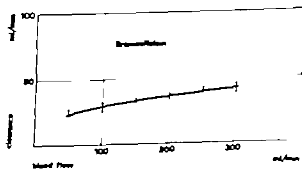


Fig 10 I vitro clearance of bromsulphalein f nction of ariable Q_B.

A New Parallel Plate Dialyser

III Preliminary Experience on Clinical Performance

S Dawids and S Vojnovic

From Department P Division of Nephrology University Hospital, Rigshospitalet Copenhagen Denmark

ABSTRACT The clinical model of new parallel plate dialyser with a membrane area of 0.96 m^2 with cuprophane 150 PM has been tested in more than 2000 dialyses with good clinical results. The simple design permits an aseptic, semiautomatic assembly and makes cheap industrial production possible Clinical clearance values for urea, creatinine and uric acid are presented as well as data for ultrafiltration, residual blood volume and rupture frequency The specific efficiency per square meter has been found to be high.

With the advent of large-scale haemodialysis treatment the need for low priced disposable equipment has become urgent A model of a semiautomatically manufactured parallel plate dialyser has been tested in more than 2000 dialyses with good biochemical and clinical results

The design and construction of the dialyser has been described earlier (2) This paper reports on our preliminary experience with a clinical model shown in Fig 1 with a dialysing area of 0 96 m^2 and sterilized by irradiation (minimum dose 3... megarad)

( ) Residual blood volume in the dialyser was determined randomly in 52 routine dialyses at the termination of the treatment. The dialysers were taken apart and the membrane was thoroughly washed together with the blood ports in 1 liter of saline The mixture was haemolysed with 2 drops of Triton X® and the absorption of filtered sample was measured spectrophotometrically at 540 μ (Beckmann Model B 17000) From the patient blood sample was taken from the venous blood line prior to the termination of dialysis. This sample was likewise haemolysed and diluted with saline to 1/125 1/250 1/500 and 1/1000 corresponding to 8 4 and 1 ml blood in 1 liter espectively From the resulting graph the quantity of blood in the washing water could be determined within 0 2 ml

The mean residual blood loss was found to be 3 1 ml (range 0.5–6.5 S.D = 1.3). As the erythrocytes trigger the coagulation cascade (1 4 7) through release of ADP it has been thought that higher haematocrit values could lead to higher clot formation with resultant larger blood loss. As shown in Fig. 2 no significant correlation to the patient s haematocrit (correlation rate = 0.007) could however be detected in the present tests

The ultrafiltration rate was recorded during a 2 hours period of dialysis with a blood flow above 150 ml/min, and was estimated from the weight reduction which was measured on a bed balance (Datex, WM 104) better than ±10 g. Transmembrane pressure (TMP) was recorded via a transducer previously described (3) and was held constant during the two hours Measurements of the relationship between TMP and ultrafiltration rate were made during 205 dialyses.

In Fig. 3 the ultrafiltration rate in ml per hour is given as a function of the transmembrane pressure The dispersion is shown as a shaded area around the mean graph which shows an ultrafiltration rate of approx 300 ml/h at a TMP of 200 mmHg and approx 1025 ml/h at a TMP of 400 mmHg.

(b) Clearance was calculated according to the conventional equation.

$$Cl = \dot{Q}_B \cdot E \quad (1)$$

and

$$E = \frac{C_{BI} - C_{Bo}}{C_{BI}} \quad (2)$$

where Cl = clearance Q_B = bloodflow E = extraction C_{BI} = blood concentration at entry and C_{Bo} = blood concentration at outlet.

In all cases an occlusive roller pump (Travenol) was used The blood flow was determined indirectly by measuring the time required for 25 revolutions of the roller pump head By relating rotation speed to a volumetric determination before and af

A New Parallel Plate Dialyser

III. *Preliminary Experience on Clinical Performance*

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The design and construction of the dialyser has been described earlier (2). This paper reports on our preliminary experience with a clinical model shown in Fig. 1 with a dialysing area of 0.96 m² and sterilized by irradiation (minimum dose 3.2 megarad).

(a) *Residual blood volume* in the dialyser was determined randomly in 52 routine dialyses at the termination of the treatment. The dialysers were taken apart and the membrane was thoroughly washed together with the blood port in 1 liter of saline. The mixture was haemolysed with 2 drops of Triton X® and the absorption of a filtered sample was measured spectrophotometrically at 540 μ (Beckmann Model B 12000). From the patient a blood sample was taken from the venous blood line prior to the termination of dialysis. This sample was likewise haemolysed and diluted with saline to 1/125, 1/250, 1/500 and 1/1000 corresponding to 8, 4, 2 and 1 ml blood in 1 liter respectively. From the resulting graph the quantity of blood in the washing water could be determined within 0.2 ml.

The mean residual blood loss was found to be 3.1 ml (range 0.5–6.5, S.D. = 1.3). As the erythrocytes trigger the coagulation cascade (1, 4, 7) through release of ADP it has been thought that higher haematocrit values could lead to higher clot formation with resultant larger blood loss. As shown in Fig. 2 no significant correlation to the patient's haematocrit (correlation rate = 0.007) could however be detected in the present tests.

The ultrafiltration rate was recorded during a 2 hours period of dialysis with a blood flow above 150 ml/min and was estimated from the weight reduction which was measured on a bed balance (Datex WM 104) better than ±10 g. Transmembrane pressure (TMP) was recorded via a transducer previously described (3) and was held constant during the two hours. Measurements of the relationship between TMP and ultrafiltration rate were made during 205 dialyses.

In Fig. 3 the ultrafiltration rate in ml per hour is given as a function of the transmembrane pressure. The dispersion is shown as a shaded area around the mean graph which shows an ultrafiltration rate of approx. 300 ml/h at a TMP of 200 mmHg and approx. 1025 ml/h at a TMP of 400 mmHg.

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$$Cl = \dot{Q}_B \cdot E \qquad (1)$$

and

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where Cl = clearance, $\dot{Q}_B$ = bloodflow, E = extraction, C_{Bi} = blood concentration at entry and C_{Bo} = blood concentration at outlet.

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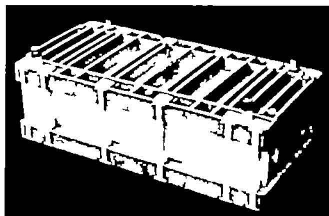


Fig 1 The prototype B of the Boe–Dawids dialyser

ter the dialysis the error was found to be within ±2.5% Blood samples were drawn simultaneously from the arterial and venous lines in 5 ml syringes These were held in an upright position for approximately 15 minutes to allow sedimentation of the erythrocytes which thereupon were returned to the blood circulation Analyses were made for urea, creatinine and uric acid in the plasma

The results are given in Figs 4–6 Clearance values are at a bloodflow of 200 ml/ml urea=122 ml/min creatinine=96 ml/min and uric acid=81 ml/min. These clearances have been measured both with single pass of 600 ml/min shown as black spots and with local recirculation of ?500 ml/min indicated by open spots It is seen that increased velocity of the dialysate results in an insignificant increase of the efficiency

Rupture frequency Blood leaks were detected in barely 2% of all dialyzers 2/3 of these were faint

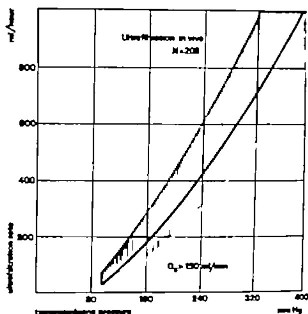


Fig 3 In vivo ultrafiltration rate as a function of TMP The shaded area covers the 98% confidence limits.

mostly transient leaks barely visible in the effluent dialysate and they were only detected because of a very sensitive blood leak monitoring system (3) With the initiation of the industrial production the variation of leaks was found to vary considerably depending on the methodology of irradiation sterilization (3 2 megarad as minimum dose) The first industrial batch of 50 dialysers resulted in 3 evident

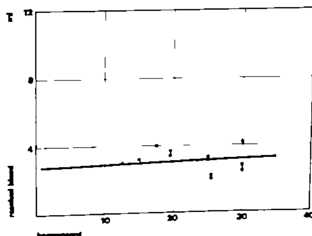


Fig 2 Residual blood volume as a function of haematocrit value No correlation to the haematocrit is present

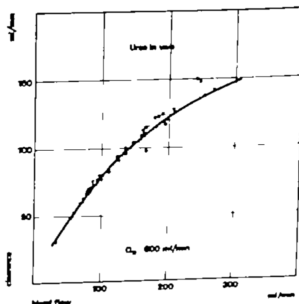


Fig 4 In vivo clearance for urea The black spot are values with single pa dialysat flow and the open spot indicate local recirculation (?.5 l/mi) added to the mentioned 600 ml fresh dialysate.

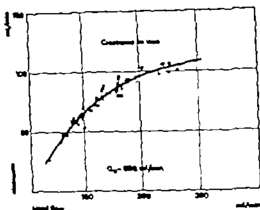


Fig 5 In vivo clearance for creatinin. For further explanation see text.

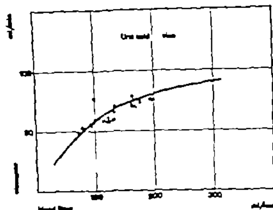


Fig 6 In vivo clearance for uric acid. For further explanation see text.

ruptures necessitating replacement of the dialyser during dialysis in two cases. A further 13 weak transient leaks were detected By sterilising over longer period of time and carefully adjusting a number of parameters primarily the moisture contents of the membrane the high incidence of the leaks has been eliminated and no blood leak has occurred during the last 500 dialyses.

DISCUSSION

The residual blood volume averaging 3 1 ml is acceptable This is obtained with combined washback with 200–300 ml saline and air An isolated air inflation without a previous saline washback will result in at least 20–40 ml extra of residual blood being lodged as a very thin (0.004 mm) layer on the entire membrane As pointed out by others a similar amount of blood is lost in the blood lines (5 6)

Considerable variations of *ultrafiltratio rate* as shown in Fig. 3 is well known clinical observation The variations from the average values are more than 10% The reasons for this fact are not only variations in the membrane properties but also individual differences in patient response in part due to deposits (proteinic or cellular) on the membrane resulting in arable onchotic pressure in the blood–membrane interface

The limited membrane area of 0 96 m² results in an efficiency which in practice equals values obtained with parallel plate dialysers with 15–20% larger area. This indicates high specific efficiency

As it is seen from the clearance values (cf Figs. 4–7) no significant improvement could be discerned by larger dialysate velocity i e recirculation which suggests that the dialysate mixing is well established already at a single pass flow of 600 ml/min.

This irradiation sterilized prototype of a dialyser has been found to be acceptable for clinical use with the sole exception of an unpredictable variation of rupture frequency a problem which has been found to be closely related to the methodology of sterilisation by irradiation. Subsequent experiments have now eliminated this problem for the present generation of the dialyser

REFERENCES

1 Born, G V R. Effects of unphysiological blood flow on circulating cells. In: Physiological and clinical aspects of oxygenator design (ed. S. Dawids & H C. Engell), p. 75 Elsevier Biomedical Press B V (Amsterdam), 1976.

Dawids, S. & Bow C A new parallel plate dialyser II. Description and in vitro performance. Acta med Scand. Suppl. 607 17 1977

3 Dawids S. Bow, C & Andreassen, M M A new hemodialysis console II Description of components. Acta med Scand 193 379 1973

4 Lindsay R. M Prentice C R. M. Burton, J A., Ferguson D & Kennedy A. C. The role of the platelet-dialysis membrane interaction in thrombus formation and blood loss during hemodialysis. Trans. Amer Soc. artif intern. Org. 19 487 1973

5 Lindsay R. M Burton, J A. King, P Davidson, J F Boddy K. & Kennedy A. C. The measurement of dialyser blood loss. Clin. Nephrol. 1 24 1973

6 Longnecker R. E Goffinet, J A. & Hendler E. D.. Blood loss during maintenance hemodialysis. Trans. Amer Soc. artif. intern. Org. 20 135 1974

7 Salzman, E. W Summation: Cellular reaction to the surface. Fed. Proc. 30(5): 1705 1971

Acta Medica Scandinavica

Supplementum 609

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University of Umeå S-901 87 Umeå 6 Sweden

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Umeå 1977

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The study cover 16 seasons and when they were examined in an unbroken succession the seasonal incidence of the disease was found to vary in a cyclical manner each cycle comprising three to four seasons Within each cycle an increase in numbe of cases from the first to the last season was found ranging from 400 to 1 600 per cent

6 When compared season for season a congruence was found between variations in seasonal incidence documented for cases of EBN in this study and variations in season l prevalence of small odents s rated by different observers and the cyclic va iations of the two phenomena studied were found to coincide

Significant differences were found between the distributions of cases of EBN registered in AC county for seasons with a eparate grade of prevalence of small rodents in northern Swed n (low middle and high or very high)

ABSTRACT

1 Incidence and prevalence of endemic benign (epidemic) nephropathy (EBN) was studied in AC county Sweden for the period 1959 - 1975 The first cases of the disease were described in 1934 Most of the Scandinavian hospitals from which subsequent cases of the disease were reported are situated north of the 60th parallel; AC county forms part of that territory (Fig 1 page 7) The county is situated just south of the Arctic circle and covers a land area of 55 400 sq km Its mean population for the period studied was 235 000

2 The mean prevalence for the period studied was 0 08 cases per 1 000 inhabitants and year (n = 267) Cases of EBN were diagnosed nearly four times as often among males as among females The maximum mean yearly prevalence for males 0 28 cases per 1 000 was found among those aged 30-39 (29 per cent of the male cases) For females the corresponding figure 0 07 cases per 1 000 was found among those aged 40-49 (25 per cent of the female cases) Only 2 6 per cent of the cases were children 15 years or younger The distribution of the population and of cases of EBN on different occupational classes was roughly an equal one The mean of the registered maximum serum creatinine concentration was higher for females than for males

3 During the period studied cases appeared in each of the 12 municipal districts of the county The domiciles of the patients were found to be distributed seemingly at random within individual municipal districts and over the county as a whole

The mean prevalence of EBN in the sparsely populated area of the county was 1 5 times that of built-up areas and twice that of towns In the thinly populated inland region it was twice that of the more densely populated coastal region The prevalence of the disease was much higher in the northernmost than in the southernmost municipal districts

In the inland region the prevalence of EBN was higher in the eastern than in the western districts

4 Information on the prevalence of small rodents in northern Sweden was sought mainly in zoological literature for the period 19 9 - 1975 The ratings of different observers for periods (seasons) ranging from May to April the following year were accumulated and the prevalence of animals within each season studied was classified as being either of a low middle or high/very high grade When examining the seasons from 1959 and onwards the prevalence of animals was found to ris and fall in a cyclical manner from a season with a low through a season with a middle to one or two season(s) with a high or very high prevalence of small rodents and always in that order For the period 1961 - 1974 four such evolutionary cycle of small rodents were discernible

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Significant diff rence were found between the distributions of ca es of EBN registered in AC county for se son with a separate gr de of prevalence of small rode ts in northern Sweden (low middle and high or very high)

7 77 per cent of the cases of EBN diagnosed in AC county during seasons when the prevalence of small rodents in northern Sweden was of a low grade appeared during the first half of these seasons For seasons when the prevalence of animals was of a middle grade the corresponding figure was 17 per cent of the cases diagnosed during these seasons and for seasons when the prevalence of small rodents was of a high or very high grade cases of EBN were diagnosed in an almost equal proportion during the first and second halves of these seasons

When cumulating the number of cases of EBN diagnosed during seasons when the prevalence of small rodents was of a separate grade the intercept with the 50th percentile of the distributions obtained for seasons when the prevalence of animals was of a low grade fell on an average four months in advance of that for distributions obtained when the prevalence of animals was of a middle grade; the corresponding intercept for distributions obtained when the prevalence of small rodents was of a high or very high grade fell in between these extremes These results might possibly be associated with changes in age distribution of animals during the evolutionary cycle of the small rodent population

8 The main results of this study were interpreted as follows The congruent variations found between seasonal incidence of endemic benign (epidemic) nephropathy in AC county and seasonal prevalence of small rodents in northern Sweden speak in favour of a close state of dependence between the two phenomena for the period studied The constantly higher prevalence of the disease among people in AC county living farther apart than among those living more closely grouped demonstrated for the period examined in this study is compatible with such an interpretation

The random geographic distribution in AC county and its municipal districts of the patients domiciles the appearance of cases during every period studied the low mean prevalence of the disease and the lack of evidence for its spreading from person to person are all findings compatible with the disease studied in this investigation being of an endemic nature in the area(s) examined

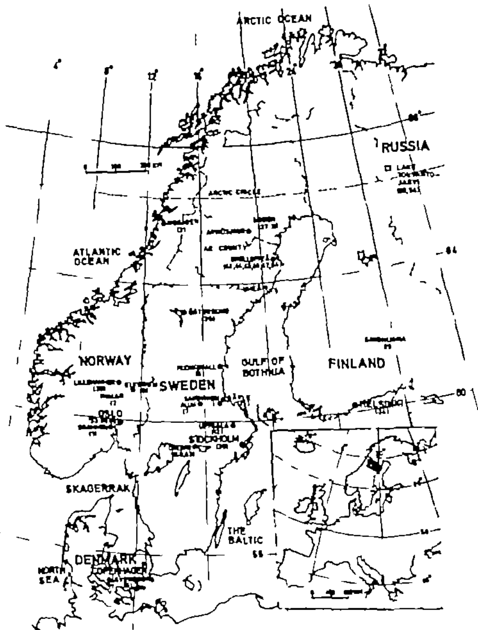


Fig 1 Contour map o Scandinavia showing the geographic position o of hospitals from which ca s of endemic benign (epidemic) nephropathy have been reported in the literature; references within brackets Boundarie of AC county where the present study was carried ont are indicated (- -) For details on distribution of cases in Finland see (29)

□ indicate approximate position of area from which outbreaks we reported among German and Fi nish troops in 1942

Ins rt map Europe H tched area Position of AC county Sweden

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I 2 Etiology of the disease and factors discussed as being of pathogenic importa ce

The symptoms and signs of EBN are strongly suggestive of the disease being of an infectious origin (37 38 44) However efforts reported by previou inve tigators to demonstrate an infectious agent in these patients have completely failed (24 29 33 38 39 50 56) but a cytopathic factor is now being investigated (19 43) Although cas s of the disease were reported among members of the same family (29 45) among people working and lodging tog ther e g lumberers (61) nd soldiers (20 54) and among those occupied in medical service (24 61) no evid nce was found in favour of the disease being spread by means of personal contacts (54) Mo t likely EBN i therefore not propagated from person to person (12 29 47) and consequently much attention has been paid to circumstan es in the patients immediate surroundings e g living or occupational condit ons when trying to explain why and how people contract the disease In his report of the outbreak in 1942 among German troops campaigning on the northern stretch of the Finnish Russian border STUHLFAUT concluded that close contact with the wet ground was of deci ive importance for contracting the dis ase (54) In papers on pidemic nephropathy several Scandina v an authors (12 32 38 61) point to the circumstance that pat ents were e counte ed who had been l ving under conditions of hygiene rated as primitive when they were truck by the diseas The wer also patients who reported having pursued some form of outdoo activity hortly before contracting the disease e g fi hing or hunt ng (33) or touri g the mountains (32) Such tiviti s as logg ng (23 24 39 60) hay making (29 40) oad (41) o il oad work (21) or picking berries in the woods or on peat land (45) have also been singled out when trying to explain why people contract EBN Such detail concerning the patient activities prior to being stru k by the disease a e usually giv n as part of case histo ies and are thus valid only for individual patients or a fraction of the material presented and it i therefore difficult to evaluate to what extent they might be rated a being of pathogenic importance; this difficulty is enhanced by our ignorance of the incub tion time

I INTRODUCTION

In 1934 ZETTERHOLM described seven patients from Skellefteå as cases of acute nephritis simulating acute abdominal disease (64) Shortly afterwards MYHRMAN published an account of likewise seven cases from Östersund of a kidney disease with peculiar symptoms and signs (36) All these patients spontaneously made an uneventful and apparently complete recovery despite having been found to have proteinuria and a raised concentration of non protein serum nitrogen

Since then a substantial number of authors have reported similar cases Gradually it became obvious that the great majority of the patients were living in that part of Scandinavia lying north of a line corresponding to the 60th parallel (Fig 1 page 7) and in that area they were found when sought for to be by no means rare (29 44 45 61) Hitherto no cases of a similar kind have been observed in Iceland (59)

I 1 The disease as an entity and its designation

Repeated efforts have completely failed to demonstrate the symptoms and signs of these patients to be the consequence of or associated with any type of disease usually seen in acutely ill individuals displaying signs of a kidney affection (24 29 50 56) Consequently the tentative suggestion (36 38) that this condition constitutes a clinical entity of its own is supported by most authors (15 23 29 45 48)

Following the reports (20 54) of an extensive outbreak among front soldiers on the northern stretch of the Finnish-Russian border of an illness similar to that seen in Sweden MYHRMAN (37) suggested the disease be named epidemic nephropathy The appropriateness of this designation has however been questioned (6 28 32 46 48) and other denominations have also been proposed (6 15 44) Some authors suggest that the disease might be endemic in northern Scandinavia (40 41 46) The proposal to classify it as a (Scandinavian) variety of (Asian) epidemic hemorrhagic fever (25) with renal syndrome is also advocated (29 45 56 60) The disease is forthwith referred to as endemic benign nephropathy (EBN) for reasons to be presented

I 2 Etiology of the disease and factors discussed as being of pathogenic importance

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The outbreak among German troops in 1942 was reported to coincide with the appearance of small rodents in great abundance within the area where the soldiers contracted their disease (54) and in subsequent reports (20 29 45 55 61) examples were presented of cases accumulating during years when voles were seen in great numbers Being a resident of or visiting those parts of (northern) Scandinavia where small rodents are common was reported (12 38 40 41 45) to increase the risk of contracting the disease and in several Scandinavian studies (9 32 46 50) attention was called to the circumstance that individual patients sometimes reported having been in more or less intimate contact with small rodents before being taken ill

I 3 Distribution of cases among the population

In a nationwide survey of hospitalized cases of epidemic nephropathy among civilians in Finland (29) 97 per cent of the patients were found to be living in the countryside a proportion significantly deviating from that (44 3 per cent) of individuals living outside built-up areas for the entire population; 70 per cent of the cases diagnosed in a circumscribed area in the south-easterly part of Finland were farmers or members of farm households In this district also the majority of the patients 95 per cent were living in the countryside

The sex ratio of EBN among civilians is reported to be highly in favour of men In a Swedish survey (47) the proportion of men was found to be 89 9 per cent (109 cases) and in Finland (29) the corresponding figure was 80 2 per cent (230 cases)

In a study of cases of EBN diagnosed within the eastern part of AC county Sweden (47) the cases were found to appear roughly in proportion to the geographic distribution of the population; the fraction of people or of patients living outside built-up areas was not reported however

I 4 Number of cases and incidence of the disease as reported in previous studies

For the period 1934 - 1974 Scandinavian authors have reported nearly 1 000 cases of the disease among civilians

Three different kinds of events may be discerned when surveying previous studies on the incidence of the disease

(a) The appearance of sporadic cases apparently isolated from each other (7 11 21 24 33 37 40 41 50 63)

(b) Outbreaks consisting of a varying but moderate number of cases (6 9 12 15 23 31 32 36 38 61 62 64) some occurring within a restricted geographic area To these may be added the singular outbreak among front soldiers on the Finnish-Russian border in 1942 probably numbering more than 2 000 cases by far the most extensive and most concentrated outbreak of the disease recorded (20 54)

(c) A variation in number of cases obvious when the incidence was studied for a sufficiently long period e g a decade or more (29 45 46 47)

An un ven intra-annual distribution of cas s was also reported (12 29 34 45) the majority appearing during autumn and early winter Furthermore c ses were repo ted to be more commonly encountered during those periods of the winter seasons when the mean out-door temperature was low i e -15^{0} Centigrad or lowe (29)

I 5 Purpose of the present investigation

Th purpose of this investigation was

(a) to tudy incidence and p evalence of endemic benign (epidemic) nephropathy and geographic distribution of cases of the di ease in AC county Sweden and its municipal districts

(b) to examine fa tors that might affect these parameters with emphasi on the influence of popul tion den ity and prevalence of small rodents

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(b) to examine factors that might affect these parameters with emphasis on th influence of population density and prevalence of small rodents

Table I Diagnoses used for selecting medical records likely to document cases of endemic benign nephropathy (EBN) Extract from WHO International classification of Diseases Injuries and causes of Death; Scandinavian editions with subdivisions added

1957		1964		1968	
049 2	Infectio acuta UNS	138 19 475 99	Infectio UNS	079 99	Infectio virosa NUD
				136 09	Infectio NUD
481	Influenza UNS	481 90	Influenza UNS	470 99	Influenza NUD
590	Nephritis acuta	590	Nephritis acuta	580 99	Glomerulonephritis acuta
593	Nephritis causa ac vel chron non indicato	593 99	Nephritis causa ac vel chron non indicato	583 99	Nephritis NUD
				590 10	Pyelonephritis acuta
				590 98	Infectio renis alii definita
600	Morbi infectiosi renum	600	Morbi infectiosi renum alia	590 99	Infectio renis NUD
				593 10	Nephrosis acuta tubularis
603	Alii morbis renis et ureteris	603 09	Morbi renis et uretoris alii UNS	593 22	Proteinuria benigna
				593 28	Morbi renis alii
				593 281	Nephropathia endemica benigna (EBN)
				593 287	Nephritis interstitialis
				593 29	Morbi renis NUD
				599 02	Infectiones tractuum urinariorum NUD
				599 09	Alii morbi tractuum urinariorum NUD
786 4	Polyuria	786 40	Polyuria	785 51	Symptomata abdominalia acuta NUD
786 5	Oliguria anuria	786 50	Oliguria	786 40	Polyuria
		786 51	Anuria	786 50	Oliguria neonati excepta
789 0	Albuminuria UNS	786 99	Symptomata organorum urogenitalium alia sive UNS	786 51	Anuria neonati excepta
789 4	Haematuria UNS			788 80	Febris incertae causae
792	Uraemia	789 09	Albuminuria	789 00	Proteinuria (albuminuria)
		789 49	Haematuria	789 30	Haematuria
		789 99	Uraemia	792 99	Uraemia
		793 90	Alii casus morbi organorum urogenitalium suspecti		

II METHODS

II 1 Documentation of cases

From the files of the departments of medicine and pediatrics and that of infectious diseases at the three hospitals in AC county those records were studied which had been made for patients finally diagnosed either as cases of epidemic n phropathy or as some of the conditions most likely to be confused with cases of EBN (Table I page 12)

Irrespective of the actual diagnosis in the records examined it was estimated whether the information obtainable from e ch one was adequate for accepting the patient as a case of EBN or not; this decision was made using the discriminating characteristics presented in Table II

Table II Criteria used for discriminating cases of EBN

1	Suddenly falling ill
2	Elevated body temperature
3	Ache and/or pa n mostly abdominal or in the back
4	Gastroint stinal symptoms
5	P oteinur a
6	Elevated concentration of serum non protein nitrogen
7	Unev ntful course
8	Spontaneous recov ry

Fo each case was recorded date of onset of illness and for c ses regi tered f om December 1959 to April 1974 also profession age se and geographic position of the patient s domcile; these demog phic data and also some of the findings recorded during the acute phase of the dise se are presented in the Appendix (Table A)

From May 1960 to April 1974 the geographic ite of the domicile was plotted for each pati nt on maps of AC county (pages 35 41) indicating whether it was situated in a sparsely populated or built up area or in a town This was done according to the official d finition of a built-up area being a place

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		475 99		136 09	Infectio NUD
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590	Nephritis acuta	590	Nephritis acuta	580 99	Glomerulonephritis acuta
593	Nephritis causa ac vel chron non indicato	593 99	Nephritis causa ac vel chron non indicato	583 99	Nephritis NUD
				590 10	Pyelonephritis acuta
				590 98	Infectio renis alii definita
600	Morbi infectiosi renum	600	Morbi infectiosi renum alia	590 99	Infectio renis NUD
				593 10	Nephrosis acuta tubularis
603	Alii morbis renis et ureteris	603 09	Morbi renis et ureteris alii UNS	593 22	Proteinuria benigna
				593 28	Morbi renis alii
				593 281	*Nephropathia endemica benigna (EBN)*
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786 4	Polyuria	786 40	Polyuria	785 51	Symptomata abdominalia acuta NUD
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		786 51	Anuria	786 50	Oliguria neonati excepta
789 0	Albuminuria UNS	786 99	Symptomata organorum urogenitalium alia sive UNS	786 51	Anuria neonati excepta
789 4	Haematuria UNS	789 09	Albuminuria	788 80	Febris incertae causae
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		789 99	Uraemia	789 30	*Haematuria*
		793 90	Alii casus morbi organorum urogenitalium suspecti	792 99	Uraemia

II 4 Small rodent field population dynamics

The account presented in this study of small rodent population dynamics was based on information sought in zoological literature (1-5 10 14 16 18 22 26 27 35 49 57) and among ecological zoologists (17 22 58)

II 4 1 General theory

Population dynamics of wild living animal are most extensively tudied in small rodents mostly voles In circumpolar regions of the northern hemisphere field populations of these animals are subject to recurring changes (18 35) which may be summarized in the following way

(a) The number of animals fluctuates in a regular manner

(b) These fluctuations may occur synchronously although with phasic shifts over a vast geographic area (1 16 35 57)

(c) When studied simultaneously an augmented amplitude of the fluctuations is usually observed on more northernly latitudes compared to those found in areas situated more to the south (16 22 27)

(d) It has become an establi hed convention (4 26 35) among ecological zoologists wh n studying the population dynamics of small rodents to survey periods tarting in spring (usually in May) when vegetation begins to sprout and continui g to April the following year In the present study this accepted custom was observed and uch a period is forthwith refer ed to as a se on

The fluctuations in number of animals to which rodent populations are subject form cyclical events (1 18 35) which are repeated every thi d to fourth year (1 16 35) four-year and also five-year ones appearing among the dominating three-year cycles (35)

During such an evolutionary cycle of small rodents the quantity of animal in a field population changes in the following order (1 5)

Starting with a season when the number of animals is at its lowest level during the cycle i e a season of low abundance there follows a season when the reproductive rate of the population is found to be considerably speeded up As the ani-

with 200 inhabitants or more and where the distance between buildings does not exceed 200 metres (42) Each site was labeled with the sequential number(s) given to the patient(s) inhabiting it

II 2 Population characteristics of AC county

For each of the 12 municipal districts into which AC county is divided detailed information was obtained for the census years of 1960 1965 and 1970 (42) on land area distribution of population according to sex and age-groups and occupational classes as well as proportion of population living in the sparsely populated and in the built-up areas respectively; for the remaining years of the period studied the number of people living outside and inside built-up areas respectively had to be calculated

Details of AC county built-up areas were obtained from an inventory made by the County Administration s Unit of Regional Economics (30) which included a map showing for 1970 their actual position and also displaying the geographic distribution of the county population in multiples of 10

To account for the very uneven geographic distribution of the county population the prevalence of EBN was studied separately for the inland region comprising the seven municipal districts where the mean population for the period studied was lower than the county mean (section III 1 2 page 20) and correspondingly for the coastal region comprising the five districts where the mean population exceeded that of the county mean for the period (section III 1 3 page 22)

II 3 Statistical methods

Most of the findings in this study were analyzed using non-parametric statistics (13 51 52) Whenever applied the type of test is mentioned in the text

II 4 Small rodent field population dyn mics

The account presented in this study of small rodent population dynamics was based on information sought in zoological literature (1-5 10 14 16 18 22 26 27 3 49 57) and among ecological zoologists (17 22 58)

II 4 1 General theory

Population dynamics of wild living animal are most extensively tudied in small rodents mostly voles In circumpolar regions of the northern hemisphere field populations of these animals are subject to recurring changes (18 35) which may be summarized in the following way

(a) The number of animals fluctuates in a regular manner

(b) These fluctuations may occur synchronously although with phasic shifts over a vast geographic area (1 16 35 57)

(c) When studied simultaneously an augmented amplitude of the fluctuations is usually observed on more northernly latitudes compared to those found in areas situated more to the south (16 22 27)

(d) It has become an establi hed convention (4 26 35) among ecological zoologists when tudying the population dynami s of small rodents to survey pe iods starting in spring (usually in May) when vegetation begins to sprout and continuing to April the following year In the present study this accepted custom was obs rved and such a period is forthwith referred to as a season

The fluctuations in number of animals to which rodent populations are ubject form cyclical events (1 18 35) which are repeated every third to fourth year (1 16 35) four-year and also five-year ones appearing among the dominating three-year cycles (35)

During such an evolutionary cycle of small rodents the quantity of animals in a field population chang s in the following order (1-5)

Starting with a season when the number of animals is at its lowest level during the cycle i e a season of low abundance there follows a season when the reproductive rate of the population is found to be considerably peeded up As the ani-

mals usually continue to breed during the second half of the season also (35) the net result will be an increase in number of voles their quantity reaching middle abundance During the following seasons the number of animals increases still further reaching high or very high abundance The number of animals may remain high also for the season to come in which case a four year cycle is formed Usually however maximum (peak) number of small rodents is reached during the third season of the evolutionary cycle

When the number of animals exceeds a critical level a change in their behaviour called dispersal is observed (4 35) consisting in a great proportion of the animals migrating into surroundings usually not inhabited by them The maximum density attained by the small rodent population varies from one evolutionary cycle to another and dispersal is more pronounced when very high levels of animals are reached (1) thus increasing the chance of their existence being generally observed creating the impression of a rodent year

In seasons of high or very high abundance the small rodent population´s reproductive capacity is reported to decline as early as during the first half of the season and consequently the population increase is halted (1 22 58) During the latter half of such a season the balance of the population is shifted for reasons hitherto obscure (1 35) and usually most of the population is wiped out because of a tremendous increase in mortality - a population crash (4 35); the stage is thus set for another evolutionary cycle to begin

II 4 2 Field population dynamics of small rodents in northern Sweden

The information on the prevalence of small rodents in northern Sweden was obtained either as ratings of the change in quantity of animals taking place between successive seasons the observers using verbal descriptions and classifying the seasonal prevalence of animals as being either low middle or high/very high - peak (10 16 17 26 27 58) or as quantitative information mostly as number of animals obtained at open field catches (14 16 22); this information was used to

indicate the change in seasonal prevalence of small rodents that took place from one season to the next

As no single observer reported observations covering every season of the period studied in this section 1957 - 1975 the varying number of individual observations for each season were accumulated and expre sed verbally using the classification accounted for in the opening paragraph of thi section

II Climate

Information on weather conditions each year in AC county for the period 1960 1974 was collected for the following meteorological variables (42); the data were omitted

1 date of the first and last day with continuously snow-covered ground;
2 number of days with snow-covered ground;
3 maximum depth of the snow-cover in cm;
4 number of day when the ground was free of snow
5 maximum and minimum amount of precipitation in mm for every month periods with and those without snow-cover being studied separately;
6 me n amount of yearly precipitation in mm;
7 maximum and minimum outdoor temperature in degree Centigr de for every month of the period

mals usually continue to breed during the second half of the season also (35) the net result will be an increase in number of voles their quantity reaching middle abundance During the following seasons the number of animals increases still further reaching high or very high abundance The number of animals may remain high also for the season to come in which case a four year cycle is formed Usually however maximum (peak) number of small rodents is reached during the third season of the evolutionary cycle

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As no single observer reported observations covering every season of the period studied in this section 1957 - 1975 the varying number of individual observations for each season were accumulated and expressed verbally using the classification accounted for in the opening paragraph of this section

II 5 Climate

Information on weather conditions each year in AC county for the period 1960 - 1974 was collected for the following meteorological variables (42); the data were omitted

1 date of the first and last day with continuously snow-covered ground;
2 numbe of days with snow-covered ground;
3 maximum depth of the snow-cover in cm;
4 number of days when the ground was free of snow;
5 maximum and minimum amount of precipitation in mm for every month periods with and those without snow-cover being studied separately;
6 mean amount of yearly precipitation in mm;
7 maximum and minimum outdoor temperature in degrees Centigr d for ev ry month of the period

III RESULTS

III 1 Prevalence of EBN in relation to differences in population density

III 1 1 AC county

Cases of EBN were recorded for everv year of the period studied (Table XI page 44) The yearlv prevalence of the dis ease (Table III page 19) was found to vary considerably but in a recurring fashion attaining maximum figures in 1963 1966 and 1970 The prevalence among people living in built-up areas varied in synchrony with the prevalence among those inhabiting the sparsely populated area of the county

The mean prevalence for the period studied was 0 071 cases per 1 000 inhabitants and year (range 0 009-0 329) In built-up areas containing 60 7 per cent of the mean county population for the period examined the corresponding figure was 0 059 (0-0 284) and in the sparsely populated area where 39 3 per cent of the mean population was resident it was 0 090 (0 011-0 428) a mean prevalence for the sparsely populated area 1 5 times that of the built-up ones

In the sparsely populated area of the county the population diminished by 36 9 per cent during the period studied while it increased by 29 9 per cent in the built-up areas The entire county population decreased by only 2 per cent during the same period Consequently the proportion of the population living in the sparsely populated area of the county diminished during the period examined from 48 per cent in 1960 to 31 per cent in 1973

A higher prevalence of EBN was registered among people living in the sparsely populated area than among those inhabiting the built-up areas for 12 of the 14 years studied (Table VI page 24) This difference was significant when tested statistically applying a one-sided hypothesis ($p < 0\ 005$ using Wilcoxon s signed rank test for paired differences)

T bl III AC county P evalence of EBN 1960 1973 among people living outside and those living i side bu lt p are s Number of cases per 1 000 inhabitant and year

Ye r	Site of domicile						AC county		
	par ly popul ted area			built up a ea			Number of		Cases per 1 000 in habit nts
	Number of		Ca per 1 000 in-habit nts	Number of		Ca es per 1 000 in-habitants			
	inhabit x 1 000	cases		inh bit x 1 000	cases		inhabit x 1 000	cases	
1960	114 8	6	0 052	124 6	3	0 024	239 4	9	0 028
61	111 6	6	0 054	128 1	0	0	239 7	6	0 025
62	108 2	8	0 074	130 4	4	0 031	238 6	12	0 050
63	103 6	11	0 106	133 2	5	0 038	236 8	16	0 068
64	100 0	5	0 050	135 0	2	0 015	235 0	7	0 030
1965	96 06	3	0 031	137 3	4	0 029	233 4	7	0 030
66	93 49	15	0 160	140 4	15	0 107	233 9	30	0 128
67	90 63	3	0 033	143 9	6	0 042	234 5	9	0 038
68	88 36	1	0 011	146 9	1	0 007	235 2	2	0 009
69	84 51	9	0 106	150 3	12	0 080	234 8	21	0 089
1970	80 11	14	0 175	153 1	13	0 085	233 2	27	0 116
71	77 09	3	0 039	156 0	5	0 032	233 1	8	0 034
72	74 23	1	0 013	159 4	3	0 019	233 6	4	0 017
73	72 44	31	0 428	161 8	46	0 284	234 2	77	0 329
Total		116			119			235	
Mean	92 51	8 29	0 090	142 9	8 50	0 059	235 4	16 79	0 071

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A higher prevalence of EBN was registered among people living in the sparsely populated area than among those inhabiting the built-up areas for 12 of the 14 years studied (Table VI page 24) This difference was significant when tested statistically applying a one-sided hypothesis ($p < 0\ 005$ using Wilcoxon s signed rank test for paired differences)

T ble III AC county Prev lence of EBN 1960 1973 among people living outside and those living inside built up a eas Number of ca e per 1 000 inhabitants and year

Year	Site of domicil: sparsely populated area — Number of inhabit x 1 000	Number of ca es	Cases per 1 000 in habitants	Built-up ar as — Number of inhabit x 1 000	Number of case	Cases per 1 000 in h bitants	AC county — Number of inhabit x 1 000	Number of cases	C ses per 1 000 in-habit nts
1960	114 8	6	0 052	124 6	3	0 024	239 4	9	0 028
61	111 6	6	0 054	128 1	0	0	239 7	6	0 025
62	108 2	8	0 074	130 4	4	0 031	238 6	12	0 050
63	103 6	11	0 106	133 2	5	0 038	236 8	16	0 068
64	100 0	5	0 050	135 0	2	0 015	235 0	7	0 030
1965	96 06	3	0 031	137 3	4	0 029	233 4	7	0 030
66	93 49	15	0 160	140 4	15	0 107	33 9	30	0 128
67	90 63	3	0 033	143 9	6	0 042	234 5	9	0 038
68	88 36	1	0 011	146 9	1	0 007	235 2	2	0 009
69	84 51	9	0 106	150 3	12	0 080	234 8	21	0 089
1970	80 11	14	0 175	153 1	13	0 085	233 2	27	0 116
71	77 09	3	0 039	156 0	5	0 032	233 1	8	0 034
72	74 23	1	0 013	159 4	3	0 019	233 6	4	0 017
73	72 44	31	0 428	161 8	46	0 284	234 2	77	0 329
Total		116			119			235	
Mean	92 51	8 29	0 090	142 9	8 50	0 059	235 4	16 9	0 071

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Table III AC county Prevalence of EBN 1960 1973 among people living outside and those living inside built p rea Numbe of c se per 1 000 inhabitants and year

Year	Sit of domi ile: sps sely populated are: Number of inhabit x 1 000	c se	Case per 1 000 in h bitants	built p a ea: Number of inhabit x 1 000	ca es	Cases per 1 000 in-habitants	AC county: Number of inhabit x 1 000	cases	Cases per 1 000 in-habitants
1960	114 8	6	0 052	124 6	3	0 024	239 4	9	0 028
61	111 6	6	0 054	128 1	0	0	239 7	6	0 025
62	108 2	8	0 074	130 4	4	0 031	238 6	12	0 050
63	103 6	11	0 106	133 2	5	0 038	236 8	16	0 068
64	100 0	5	0 050	135 0	2	0 015	235 0	7	0 030
1965	96 06	3	0 031	137 3	4	0 029	233 4	7	0 030
66	93 49	15	0 160	140 4	15	0 107	233 9	30	0 128
67	90 63	3	0 033	143 9	6	0 042	234 5	9	0 038
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69	84 51	9	0 106	150 3	12	0 080	234 8	21	0 089
1970	80 11	14	0 175	153 1	13	0 085	233 2	27	0 116
71	77 09	3	0 039	156 0	5	0 032	233 1	8	0 034
72	74 23	1	0 013	159 4	3	0 019	233 6	4	0 017
73	72 44	31	0 428	161 8	46	0 284	234 2	77	0 329
Total		116			119			235	
Mean	92 51	8 29	0 090	142 9	8 50	0 059	235 4	16 79	0 071

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The mean prevalence for the period studied was 0 071 cases per 1 000 inhabitants and year (range 0 009-0 329) In built-up areas containing 60 7 per cent of the mean county population for the period examined the corresponding figure was 0 059 (0-0 284) and in the sparsely populated area where 39 3 per cent of the mean population was resident it was 0 090 (0 011-0 428) *a mean prevalence for the sparsely populated area 1 5 times that of the built-up ones*

In the sparsely populated area of the county the population diminished by 36 9 per cent during the period studied while it increased by 29 9 per cent in the built-up areas The entire county population decreased by only 2 per cent during *the same period Consequently* the proportion of the population living in the sparsely populated area of the county diminished during the period examined from 48 per cent in 1960 to 31 per cent in 1973

A higher prevalence of EBN was registered among people living in the sparsely populated area than among those inhabiting the built-up areas for 12 of the 14 years studied (Table VI page 24) This difference was significant when tested statistically applying a *one-sided hypothesis* ($p < 0\ 005$ using Wilcoxon s signed rank test for paired differences)

Table IV Inl nd egion Prevalence of EBN 1960 1973 in the seven municipal di tricts of AC co nty i wh h the me n popul tion density for the period fall below that of the cou ty mean Number of ca e per 1 000 inhabitants and year among people living outside and tho e liv ng ide the bu lt up reas

Year	B te of domicile						Inland region		
	pa ely populated area			built p areas			Number of		C es per 1 000 in-habitant
	Number of		Cases pe 1 000 in habitant	Number of		Cases per 1 000 in-h bitants			
	inhabit x 1 000	cases		inhabit x 1 000	ases		inhabit x 1 000	cases	
1960	49 71	2	0 040	29 34	0	0	79 05	2	0 025
61	48 20	4	0 083	29 90	0	0	78 10	4	0 051
62	46 50	5	0 108	29 80	1	0 034	76 30	6	0 079
63	45 58	8	0 176	30 91	3	0 097	76 50	11	0 144
64	43 71	1	0 023	30 90	1	0 032	74 61	2	0 027
1965	40 83	1	0 024	29 94	1	0 033	70 77	2	0 028
66	40 28	9	0 223	30 60	8	0 261	70 88	17	0 240
67	38 96	1	0 026	30 77	2	0 065	69 73	3	0 043
68	37 86	1	0 026	30 96	0	0	68 82	1	0 015
69	36 11	7	0 194	31 45	3	0 095	67 56	10	0 148
1970	33 05	7	0 212	31 48	6	0 191	64 53	13	0 201
71	31 40	1	0 032	32 00	1	0 031	63 40	2	0 032
72	30 43	1	0 033	32 58	1	0 031	63 01	2	0 032
73	29 44	20	0 679	33 10	16	0 483	62 54	36	0 576
Total		68			43			111	
Mean	39 43	4 86	0 123	30 98	3 07	0 099	70 41	7 93	0 113

III 1 2 The inland region

The inland region was inhabited by 29 4 per cent of the mean county population for the period studied being dispersed over an area of 41 964 sq km (75 8 per cent of the county land area) The mean population density of the seven municipal districts of the region was 1 7 inhabitants per sq km (range 0 6 -3 4) being 4 2 for the entire county (Appendix Table C)

The prevalence of EBN within the region was found to vary as for the whole county (section III 1 1) attaining maximum values in 1963 1966 and 1970 the variations in the sparsely populated area and in the built-up ones being congruent (Table IV page 21)

The mean prevalence of EBN in the region for the period studied was 0 113 cases per 1 000 inhabitants and year (range 0 015-0 576) a figure 1 6 times higher than the corresponding one for the whole county In built-up areas of the region the mean prevalence was 0 099 (0-0 483) and in the sparsely populated area it was 0 123 (0 023-0 679) the latter figure being 1 2 times higher than the former

The population of the entire region diminished during the period studied by 20 9 per cent and that of its sparsely populated area by 40 8 per cent while it increased in the built-up areas of the region by 12 8 per cent The proportion of the population living in the sparsely populated area of the region diminished from 62 9 per cent in 1960 to 47 1 per cent in 1973 i e by 15 8 per cent while the proportion inhabiting the built-up areas increased as much from 37 1 to 52 9 per cent

A higher prevalence of EBN was registered among people living outside than among those living inside the built-up areas of the inland region for 10 of the 14 years studied (Table VI page 24) This difference was significant when tested statistically applying a one-sided hypothesis ($p < 0$ 05 using Wilcoxon s signed rank test for paired differences)

Tabl IV Inl nd reg on P evalance of EBN 1960 1973 in the seven municipal d striots of AC county in which th mean populatio density for the period fell below that of the county mean Number of c es per 1 000 inhabitants and y among people living outside and those living inside the built up areas

	Sit f domicile								
	par aly popul ted a es			built up e			inland region		
	Number of			Number of			Number of		
Year	inhabit x 1 000	case	Case per 1 000 in habitant	inhabit x 1 000	cases	Cases per 1 000 in habitants	inhabit x 1 000	cases	Ca es per 1 000 in habitants
1960	49 71	2	0 040	29 34	0	0	79 05	2	0 025
61	48 20	4	0 083	29 90	0	0	78 10	4	0 051
62	46 50	5	0 108	29 80	1	0 034	76 30	6	0 079
63	45 58	8	0 176	30 91	3	0 097	76 50	11	0 144
64	43 71	1	0 023	30 90	1	0 032	74 61	2	0 027
1965	40 83	1	0 024	29 94	1	0 033	70 77	2	0 028
66	40 28	9	0 223	30 60	8	0 261	70 88	17	0 240
67	38 96	1	0 026	30 77	2	0 065	69 73	3	0 043
68	37 86	1	0 026	30 96	0	0	68 82	1	0 015
69	36 11	7	0 194	31 45	3	0 095	67 56	10	0 148
1970	33 05	7	0 212	31 48	6	0 191	64 53	13	0 201
71	31 40	1	0 032	32 00	1	0 031	63 40	2	0 032
72	30 43	1	0 033	32 58	1	0 031	63 01	2	0 032
73	29 44	20	0 679	33 10	16	0 483	62 54	36	0 576
Total		68			43			111	
Mean	39 43	4 86	0 123	30 98	3 07	0 099	70 41	7 93	0 113

III 1 3 The coastal region

The coastal region of AC county covers an area of 13 432 sq km (24 2 per cent of the county land area) and was inhabited by 70 6 per cent of the mean county population for the period studied The mean population density of the five municipal districts of the region was 12 2 inhabitants per sq km (range 6 6-27 9 Appendix Table C) The prevalence of EBN in the sparsely populated area of the region attained maximum values in 1964 1966 and 1970 and in the built-up ones in 1962 1966 and 1969 (Table V page 23) For the whole region maximum prevalence figures of EBN were attained in 1962 1966 and 1970 i e for the same years as for the inland region (section III 1 2) and for the entire county (section III 1 1) with 1962 as an exception

The mean prevalence of EBN for the whole region was 0 054 cases per 1 000 inhabitants and year for the period studied (range 0 006-0 239) a figure 0 76 of the county mean and 0 48 of that for the inland region In built-up areas the corresponding figure was 0 049 (0-0 233) and in the sparsely populated area it was 0 065 (0-0 256) the latter figure being 1 3 times as high as the former For the entire region a population increase of 7 1 per cent was noted for the period studied and for the built-up areas of the region the population figure rose by 35 2 per cent For the sparsely populated area the population decreased by 34 per cent

The proportion of the population inhabiting the sparsely populated area of the region diminished by 15 6 per cent during the period studied from 40 6 per cent in 1960 to 25 0 per cent in 1973 and rose for the built-up areas by a corresponding amount from 59 4 per cent in 1960 to 75 0 per cent in 1973

A higher prevalence of EBN was registered among people living outside than among those living inside the built-up areas of the coastal region for 11 of the 14 years studied (Table VI page 24) a significant difference when tested statistically applying a one-sided hypothesis ($p < 0\ 025$ using Wilcoxon s signed rank test for paired differences)

Table V Coastal region P eval nce of EBM 1960 1973 in the five municipal district of AC ounty in which the mean population density for the period fell above that of th county mean Number of case per 1 000 inhabitants and year among people living out- ide and tho e li ing inside the built up ar as

Year	Site of domi ile								
	Sparsely populated area			built up reas			coa tal region		
	Number of			Number of			Number of		
	inhabit x 1 000	cases	Cases per 1 000 in-habitant	inhabit x 1 000	cases	Cases per 1 000 in-habitant	inhabit x 1 000	cases	Cases por 1 000 in h bitants
1960	65 11	4	0 061	95 19	3	0 032	160 3	7	0 044
61	63 40	2	0 032	98 20	0	0	161 6	2	0 012
62	61 70	3	0 049	100 6	3	0 030	162 3	6	0 037
63	58 01	3	0 052	102 3	2	0 020	160 3	5	0 031
64	56 32	4	0 071	104 1	1	0 010	160 4	5	0 031
1965	55 23	2	0 036	107 4	3	0 028	162 6	5	0 031
66	53 21	6	0 113	109 8		0 064	163 0	13	0 080
67	51 67	2	0 039	113 1	4	0 035	164 8	6	0 036
68	50 50	0	0	115 9	1	0 009	166 4	1	0 006
69	48 40	2	0 041	118 8	9	0 076	167 2	11	0 066
1970	47 06	7	0 149	121 6	7	0 058	168 7	14	0 083
71	45 69	2	0 044	124 0	4	0 032	169 7	6	0 035
72	43 80	0	0	126 8	2	0 016	170 6	2	0 012
73	43 00	11	0 256	128 7	30	0 233	171 7	41	0 239
Total		48			76			124	
Mean	53 08	3 43	0 065	111 9	5 43	0 049	165 0	8 86	0 054

III 1 3 The coastal region

The coastal region of AC county covers an area of 13 432 sq km (24 2 per cent of the county land area) and was inhabited by 70 6 per cent of the mean county population for the period studied The mean population density of the five municipal districts of the region was 12 2 inhabitants per sq km (range 6 6-27 9 Appendix Table C) The prevalence of EBN in the sparsely populated area of the region attained maximum values in 1964 1966 and 1970 and in the built-up ones in 1962 1966 and 1969 (Table V, page 23) For the whole region maximum prevalence figures of EBN were attained in 1962 1966 and 1970 i e for the same years as for the inland region (section III 1 2) and for the entire county (section III 1 1) with 1962 as an exception

The mean prevalence of EBN for the whole region was 0 054 cases per 1 000 inhabitants and year for the period studied (range 0 006-0 239) a figure 0 76 of the county mean and 0 48 of that for the inland region In built-up areas the corresponding figure was 0 049 (0-0 233) and in the sparsely populated area it was 0 065 (0-0 256) the latter figure being 1 3 times as high as the former For the entire region a population increase of 7 1 per cent was noted for the period studied and for the built-up areas of the region the population figure rose by 35 2 per cent For the sparsely populated area the population decreased by 34 per cent

The proportion of the population inhabiting the sparsely populated area of the region diminished by 15 6 per cent during the period studied from 40 6 per cent in 1960 to 25 0 per cent in 1973 and rose for the built-up areas by a corresponding amount from 59 4 per cent in 1960 to 75 0 per cent in 1973

A higher prevalence of EBN was registered among people living outside than among those living inside the built-up areas of the coastal region for 11 of the 14 years studied (Table VI page 24) a significant difference when tested statistically applying a one-sided hypothesis ($p < 0\ 025$ using Wilcoxon s signed rank test for paired differences)

III 1 4 Differences between areas and regions of AC county

In Table VI (page 24) are presented in number of cases per 1 000 inhabitants and ye r the differences in prevalence of EBN analysed in section III I 1 -3 of this study Also calculated were those differences obtained when subtracting the prevalence of the dise se in the sparsely populated area of the coastal region from that of the inland region ($p < 0\ 005$) the prevalence of EBN in the built up areas of these regions re- pectively ($p < 0\ 02$) and finally the difference in the prevalence of the dis ase obtained between the entire inland and coastal reg on ($p < 0\ 005$)

When studied from December 1959 to April 1974 the mean prevalen e of EBN among people living in the thinly populated nland region of AC county was found to exceed that among those inhab ting the more densely populated coastal region Such was the case not only when studying the prevalence in the sparsely populated area of each region but also when separately investigating built up ar as other than towns and (central parts of) town espe tively of each region (Table VII page 26)

51 3 per cent of the total number of cases of EBN examined in detail we e diagnosed among people living in the sparsely populated are of AC county 30 0 pe cent among those inhabiting bu lt-up rea othe th towns and 18 7 per cent among town dweller espectively

III 2 D stribut on of case according to sex, age-groups and occupational cla ses

III 2 1 Sex

The ave g r t o of men to women was for the material examined n detail 3 5 being 3 0 for cases di gnosed among people l ving in the sparsely populated a ea of the county 3 2 among town-dweller and 4 7 for people inhabiting built-up are- a other than towns (Table VIII page 27) The ratio between males and female was lowest 2 0 in the only town of the in land reg on (Lycksele) and highest 5 0 among people inhabiting built-up areas other than towns in the coastal region of the county

ble VI Differences in prevalence of EBN in AC county 1960 - 1973 for areas and regions of different population density as defined in the text Number of cases per 1 000 inhabitants and year
p values denote the probability that the series of differences might be the consequence of chance variation (Wilcoxon s signed rank test for paired differences)

	Prevalence of EBN Difference between					
	sparsely populated area and built-up areas of			inland and coastal region		
ar	AC county	inland region	coastal region	sparsely populated area	built-up areas	the regions
960	0 028	0 040	0 029	-0 021	-0 032	-0 019
61	0 054	0 083	0 032	0 051	0	0 039
62	0 043	0 074	0 019	0 059	0 004	0 042
63	0 068	0 079	0 032	0 124	0 077	0 113
64	0 035	-0 009	0 061	-0 048	0 022	-0 004
965	0 002	-0 009	0 008	-0 012	0 005	-0 003
66	0 053	-0 038	0 049	0 110	0 197	0 160
67	-0 009	-0 039	0 004	-0 013	0 030	0 007
68	0 004	0 026	-0 009	0 026	-0 009	0 009
69	0 026	0 099	-0 035	0 153	0 019	0 082
1970	0 090	0 021	0 091	0 063	0 133	0 118
71	0 007	0 001	0 012	-0 012	-0 001	-0 003
72	-0 006	0 002	-0 016	0 033	0 015	0 020
73	0 144	0 196	0 023	0 423	0 250	0 337
P	0 005	< 0 05	< 0 025	< 0 005	< 0 025	< 0 005

III 1 4 Differences betwee_ areas and regions of AC county

In Table VI (page 24) are presented in number of cases per 1 000 inhabitants and year the differences in prevalence of EBN analysed in section III 1 1 -3 of this study Also calculated were those differences obtained when subtracting the prevalence of the diseas in the sparsely populated area of the coastal r gion from that of the inland region ($p < 0.005$) the prevalence of EBN in the built up areas of these regions respectively ($p < 0.025$) and finally the difference in the p evalence of th disease obtained between the entire inland and coastal region ($p < 0.005$)

When tudied from Dec mber 1959 to April 1974 the mean p evalence of EBN among people living in the thinly populated inland region of AC county was found to exceed that among those inhabiting the more d nsely populated coastal region Such was the case not only when study ng the prevalence in the sparsely populated area of each region but also when separately investigating built up areas other than towns and (central parts of) towns respectively of each region (Table VII page 26)

51 3 per cent of the total number of cases of EBN examined n detail were diagnosed among people l ving in the sparsely popul ted ar a of AC county 30 0 per cent among those inhabit- i g bu lt-up are s other than towns and 18 7 per cent among town-dweller espect vely

III 2 D stribut on of cases according to sex, age-groups and occupational classe_

III 2 1 Sex

The verage tio of men to women wa for the material examined in detail 3 5 be ng 3 0 for case diagnosed among people liv ng in the parsely populated area of the county 3 2 among town-dweller and 4 7 for people inhabiting built up areas oth r than towns (Table VIII pag 27) The ratio between male and females w s lowe t 2 0 in the only town of the inland region (Lycksele) and highest 5 0 among people inhabiting built up areas oth r than towns in the coastal region of the county

Table VI Differences in prevalence of EBN in AC county 1960 - 1973 for areas and regions of different population density as defined in the text Number of cases per 1 000 inhabitants and year

p values denote the probability that the series of differences might be the consequence of chance variation (Wilcoxon s signed rank test for paired differences)

Prevalence of EBN Difference between

	sparsely populated area and built-up areas of			inland and coastal region		
Year	AC county	inland region	coastal region	sparsely populated area	built-up areas	the regions
1960	0 028	0 040	0 029	-0 021	-0 032	-0 019
61	0 054	0 083	0 032	0 051	0	0 039
62	0 043	0 074	0 019	0 059	0 004	0 042
63	0 068	0 079	0 032	0 124	0 077	0 113
64	0 035	-0 009	0 061	-0 048	0 022	-0 004
1965	0 002	-0 009	0 008	-0 012	0 005	-0 003
66	0 053	-0 038	0 049	0 110	0 197	0 160
67	-0 009	-0 039	0 004	-0 013	0 030	0 007
68	0 004	0 026	-0 009	0 026	-0 009	0 009
69	0 026	0 099	-0 035	0 153	0 019	0 082
1970	0 090	0 021	0 091	0 063	0 133	0 118
71	0 007	0 001	0 012	-0 012	-0 001	-0 003
72	-0 006	0 002	-0 016	0 033	0 015	0 020
73	0 144	0 196	0 023	0 423	0 250	0 337
p	< 0 005	< 0 05	< 0 025	< 0 005	< 0 025	< 0 005

Table VIII Total number of men and women diagnosed as cases of EBN in AC county December 1959 - April 1974 in areas and regions of different population density. The ratio of males (M) to females (F) is given within brackets

	Areas of AC county classified according to population density as being			
Region	sparsely populated	built-up areas other than towns	towns central parts	The entire region/county
	M/F	M/F	M/F	M/F
Inland	56/16(3 5)	31/7 (4 4)	4/2 (2 0)	91/25(3 6)
Coastal	47/18(2 6)	35/7 (5 0)	34/10(3 4)	116/35(3 3)
AC county	103/34(3 0)	66/14(4 7)	38/12(3 2)	207/60(3 5)

III 2 2 Age-groups

In the lower half of Fig 2 (page 28) is shown separately for each sex the distribution according to age-groups of the mean number of people in the census years of 1960 1965 and 1970 inhabiting the spa ely populated are of AC county and the built up areas respectively (42) Within the different age-groups of both sexe the number of people living in built-up areas wa found to exceed the number inhabiting the sparsely populated area of the county male older than 50 years being an except on

In the upper half of Fig 2 wa plotted the mean preva lence of EBN as registered from December 1959 to April 1974 a mong each ub-group of people presented in the lower half of th f gure The mean prevale ce of the disease among the proportion of people living in the sparsely populated area of the county was found to exceed that among the corre ponding proportion of people inhabiting the built up areas within each age-group examined for females as well as for males

able VII Prevalence of EBN in AC county December 1959 - April 1974 among people living outside those living inside built-up areas other than towns and among town-dwellers respectively in regions of varying mean population density; mean number of cases per 1 000 inhabitants and year for the period studied

	Areas of AC county classified according to their population density as being											
	sparsely populated			built-up areas other than towns			towns central parts			The entire region/county		
Region	Mean number of inhabit x 1 000	Total number of cases	Mean yearly prevalence	Mean number of inhabit x 1 000	Total number of cases	Mean yearly prevalence	Mean number of inhabit x 1 000	Total number of cases	Mean yearly prevalence	Mean number of inhabit x 1 000	Total number of cases	Mean yearly prevalence
Inland	41 2	72	0 121	23 3	38	0 113	7 0	6	0 060	71 5	116	0 113
Coastal	55 8	65	0 081	44 9	42	0 065	63 2	44	0 048	163 9	151	0 064
AC county	97 0	137	0 098	68 2	80	0 081	70 2	50	0 049	235 4	267	0 079

For the sp rsely populated area of the county the mean prevalence of the disease was found for both sexes to increase with increasing age of the patients attaining a maximum for females as well as for males aged 30-39 years then diminishing gradually as the age of the patients increased further For the built up areas the mean prevalence among males also rose gradually reaching a maximum among men aged 20-29 years then diminishing; the distribution obtained for females in built-up ar as was bimodal

The maximum mean prevalence for males 0 282 cases per 1 000 men and year was observed among those aged 30 39 years; 29 per cent of the male cases were diagnosed in this age-group which made up 12 3 per cent of the mean male population for the period studied The corresponding prevalence figure for females 0 068 was found among those aged 40-49 years 25 per cent of the female c ses were diagnosed in that age-group which constituted 13 3 per cent of the mean female population for the period (Appendix Table B)

When surveying within the different age-groups examined the ratio of the proportion of cases of EBN to the corresponding proportion of the mean county population for the period studied cases were found to be proportionately more often dignosed among people 20 49 years of age and proportionately le s often among those younger than 20 or older than 49 With some exceptions this was the ca e for females as well as for males also when studying the ratio separately for members of both sexes living outside and fo those living inside built-up areas (Table IX page 30 Appendix Table B)

III 2 3 Occupation

72 7 per cent of the case of EBN in AC county were diagosed among that proportion of the population professionally engaged in occupations of some kind when truck by the disease (Table X page 31 item 1 6) For these occupational classe the proportion of cases of EBN exceeded the proportion they amounted to of the entire county population people engaged in medical service being an exception

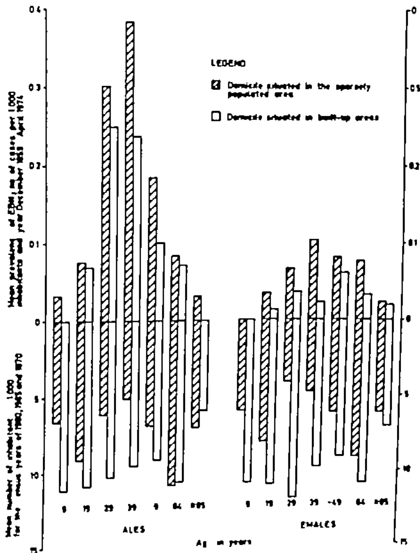


Fig 2 Distribution of the county population for the census years of 1960 1965 and 1970 (lower half) and of the prevalence of EBN in AC county December 1959 - April 1974 in number of cases per 1 000 inhabitants and year (upper half) lean alues for each age-group examined and for males and females living outside and inside built-up areas respectivel,

For the sparsely populated area of the county the mean prevalence of the disease was found for both sexes to increase with increasing age of the patients attaining a maximum for females as well as for males aged 30 39 years then diminishing gradually as the age of the patients increased further For the built up areas the mean prevalence among males also ro e gradually reaching a maximum among men aged 20-29 years then diminishing; the distribution obtained for females in built-up areas was bimodal

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III 2 3 <u>Occupation</u>

72 7 per cent of the cases of EBN in AC county were diagnosed among that proportion of the population profe sionally eng ged in occupations of some kind when struck by the disease (Table X page 31 tem 1 -6) For these occupational classes the proportion of cases of EBN exceeded the proportion they a mounted to of the entire county population people engaged in medic l service being an exception

Table IX Ratio of proportion of cases of EBN diagnosed December 1959 - April 1974 to proportion of county population (mean for 1960 1965 and 1970) for males and females in different age-groups living outside (SP) and inside (BU) built-up areas in AC county (AC)
- the proportion of cases fell below or + above that of the population
For details see Appendix (Table B)

Age group	Males			Females			Both sexes		
	Area			Area			Area		
	SP	BU	AC	SP	BU	AC	SP	BU	AC
- 9	-	-	-	-	-	-	-	-	-
- 19	-	-	-	-	-	-	-	-	-
- 29	+	+	+	+	+	+	+	+	+
- 39	+	+	+	+	-	+	+	+	+
- 49	+	-	+	+	+	+	+	+	+
- 64	-	-	-	+	+	+	-	-	-
≥ 65	-	-	-	-	-	-	-	-	

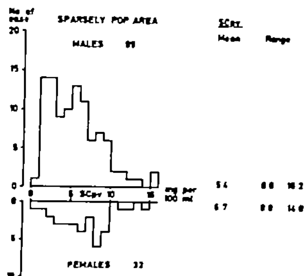
III 3 Distribution of maximum serum creatinine concentration

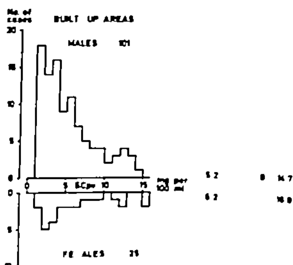
During the acute phase of EBN a transient rise in concentration of the components forming the serum non-protein nitrogen was registered for 93 7 per cent of the males and for 96 7 per cent of the females (Appendix Table A) Fig 3 (page 32) shows the distribution between the sexes of the maximum registered creatinine concentration in mg per 100 ml of serum The mean values for males did not differ between men inhabiting the sparsely populated area of AC county and those living in the built-up ones nor was any difference in corresponding mean values found between women living in those two areas of different population density

A higher mean of the maximum serum creatinine concentration registered during the acute phase of the disease was found among females than among males both for that part of the population inhabiting the sparsely populated area of the county and

Table X Distribution of cases of EBH diagnosed in AC county December 1959 - April 1974 among different categories of the county population

Population ≥ 16 years Occupation or activity	number	per cent	Cases of EBH number	Cases of EBH per cent
1 Forestry and farming	17 156	7 4	50	18 7
2 Manufacturing industry and equivalent branches	20 694	8 9	52	19 5
3 Construction	10 394	4 5	20	7 5
4 Commerce and trade communication private services	26 229	11 2	41	15 4
5 Public administration and service	10 394	4 5	24	9 0
6 Med cal service	6 443	2 8	7	2 6
Total 1 6	91 300	39 3	194	72 7
7 Students	47 600	20 4	18	6 7
8 Housewiv s	36 400	15 6	32	12 0
9 Unspecified and no information	4 700	2 0	16	6 0
Total 7 9	88 700	38 0	66	24 7
10 Child en ≤ 1 years	53 200	22 7	7	2 6
Total 1 10	233 200	100 0	267	100 0





<u>Fig 3</u> Maximum concentration of creatinine registered in mg per 100 ml of serum (SCpv) Distribution among male and female cases of EBN diagnosed in AC county December 1959 - April 1974 for those inhabiting the sparsely populated area of the county and those living in the built-up ones

for that part living in the built-up ones This difference between the sexes was significant when tested statistically ($p < 0.001$ using Student s t test)

III 4 Geographic distribution of cases

Figs 4-8 (pages 35-41) show the geographic position of the domicile for each patient diagnosed as a case of EBN in AC county from May 1960 to April 1974 for seasons each of which last from May one year to the following April

The domiciles were found to be scattered over areas of very different sizes The 12 cases diagnosed during season 1960 61 (Fig 4 page 35) and the seven diagnosed during season 1968 69 (Fig 7b page 39) appeared among the inhabitants of two of the county s twelve municipal districts situated in the eastern part of the county and bordering on each other During the majority of seasons the domiciles were spread out fairly evenly over the entire county even during seasons when comparatively few cas s were diagnosed (Fig 5a page 35 Fig 7a page 38)

When surveying the chronological order in which the cases appeared during each season studied no geographic concentration of ca s n the sense of loc lized outbreaks could be discerned

Four instances where family members contracted EBN within hort time of one another were encountered (Appendix T ble A) Cases 75 and 80 and 129 and 131 were brothers who fell ill with n two week of one another cases 174 176 and 177 were son mothe and father who contracted EBN within n interval of one and a half and one week respectively and cases 22 and 231 were father and daughter who fell ill within one week of one another All these cases were living in the sparsely populated area of the county

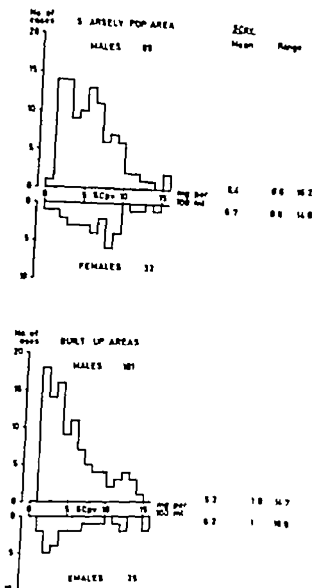


Fig 3 Maximum concentration of creatinine registered in mg per 100 ml of serum (SCpv) Distribution among male and female cases of EBN diagnosed in AC county December 1959 - April 1974 for those inhabiting the sparsely populated area of the county and those living in the built-up ones

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When survey ng the chronological order in which the cases appeared during e ch season studied no geographic concentrat on of cases in the sense of localized outbreaks could be discerned

Four instances where family members contracted EBN within a short time of one another were encountered (Appendix Table A) Cases 75 and 80 and 129 and 131 were brothers who fell ill within two weeks of one another cases 174 176 and 177 were son mother and father who contracted EBN within an interv l of one and a half and one week respectively and cases 227 and 231 were father and daughter who fell ill within one week of one anoth r All these cases were living in the sparsely populated area of the county

The mean prevalence of EBN within each of the county s twelve municipal districts was found to vary from 0 02 to 0 21 cases per 1 000 inhabitants and year for the period studied - a ten-fold difference

The mean for the eight districts in the central northern and eastern parts of the county fell above or slightly below the county mean for the period examined whereas for the four districts in the southern part of the county it fell well below that mean For the seven districts comprising the inland region the mean prevalence of EBN for the period was 1 8 times higher than for the five districts comprising the coastal region (Fig 9 page 42 Appendix Table C)

Figs 4 -8 (pages 35-41) Geographic positions of the domiciles for cases of EBN diagnosed in AC county May 1960 - April 1974 The sequential number given to each case (Appendix Table A) is attached to the domicile of the patient

On each map are plotted cases of EBN diagnosed during one season lasting from May one year to the following April (cf section II 4 and III 6 -7)

The actual prevalence of small rodents in northern Sweden during each season of the period studied (Table XII page 48) is indicated successively within the quadrangles above the map: L - low M - middle H - high and VH - very high

Domicile situated in the sparsely populated area of the county (x) in a built-up area other than town (o) or in a town (•)

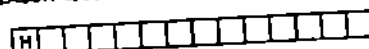


Fig 4; legend on page 34



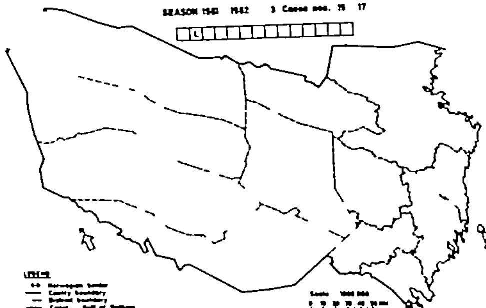


Fig 5 a; leg nd on page 34

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Domicile situated in the sparsely populated area of the county (x) in a built-up area other than town (o) or in a town (•)

Fig 6 a; legend on page 34

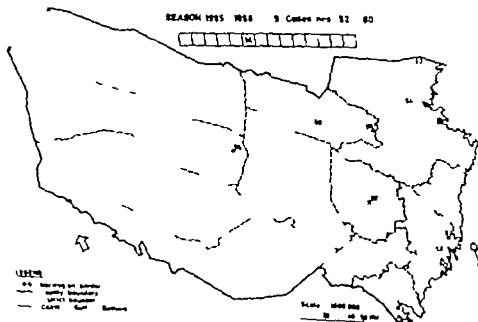


Fig 6 b; legend on

SEASON 1962 1963 n 11 Cases nos. 18 28

M

LEGEND

Coast of Gulf of Bothnia

Fig 5 b; legend on page 34

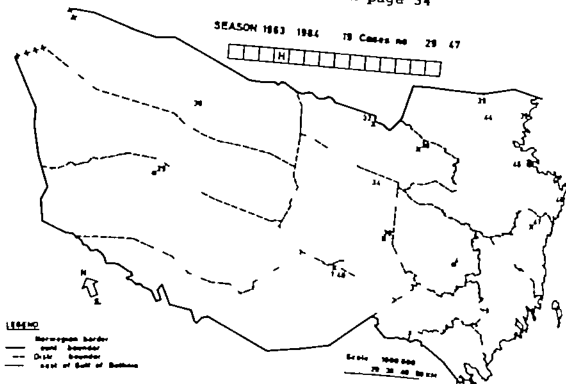


Fig 5 c; legend on page 34

Fig 6 a; legend on page 34

Fig 6 b; legend

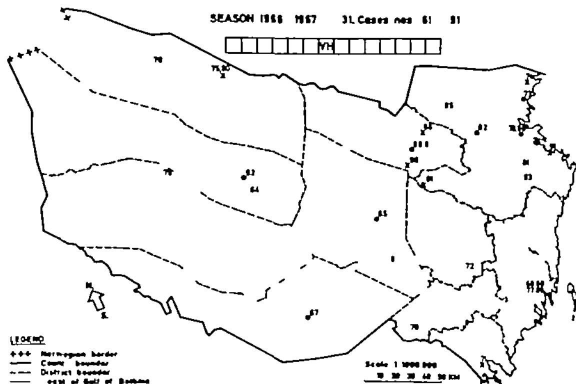


Fig 6 c; legend on page 34

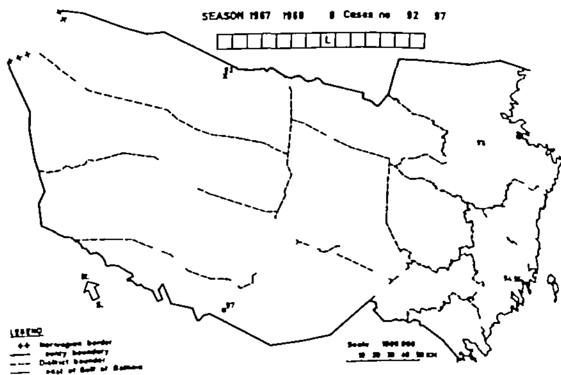


Fig 7 a; legend on page 34

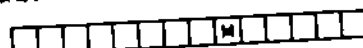


Fig 7 b; legend on page 34

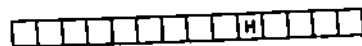


Fig 7 c; legend on page 34

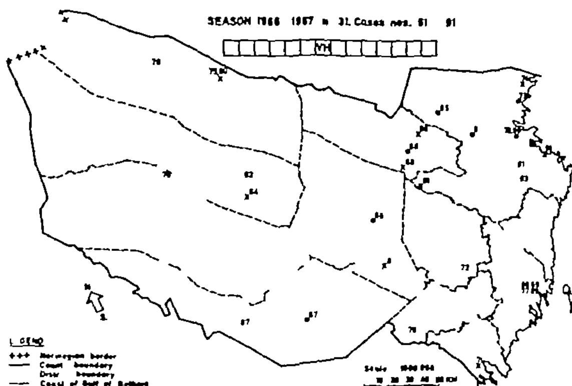


Fig 6 c; legend on page 34

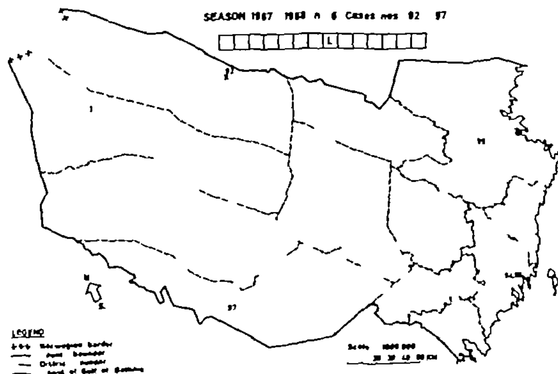


Fig 7 a; legend on page 34



Fig 8 b; legend on page 34

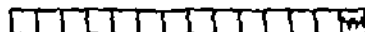


Fig 8 c; legend

SEASON 1970 1971 n 24 Cases nos 126 149

H

LEGEND

Fig 7 d; legend on page 34

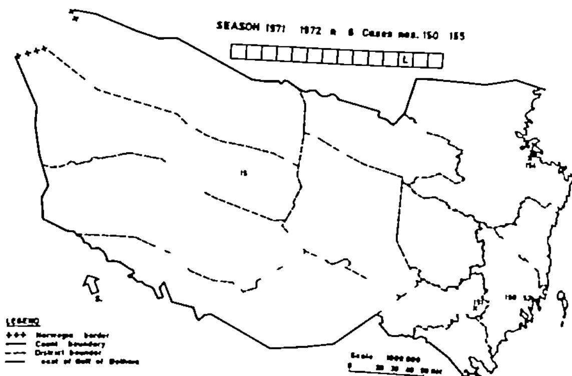


Fig 8 a; legend on page 34

III 5 Incidence of EBN

III 5 1 Monthly incidence

Table XI (page 44) shows the incidence (nos of cases registered) of EBN in AC county for the period 1959 - 1975

The median incidence of EBN as observed in AC county was two cases per month for the period studied The probability of the observed variation in monthly incidence being random was very small (Z = 5 83; p < 0 001); the hypothesis was tested by analyzing the sequence of events obtained when studying to what extent the number of cases registered each month (Table XI page 44) fell above or below the median a run test (13)

III 5 2 Quarterly incidence

18 0 per cent of the cases of EBN were diagnosed during the first 10 8 per cent during the econd 30 5 per cent during the third and 40 7 per cent during the fourth quarter of the year

III 5 3 Yea ly incidence

Case of EBN were diagnosed for every year of the period studied but in a varying number ranging from two cases in 1959 and 1968 to 92 in 1974

III 5 4 Seasonal incidence

Subsequently the incid nce of EBN in AC county was studied fo seasons each lasting from May one year to the follow ing April i e for per ods ident cal to those for which information on prev l nce of small rodents in northern Sweden was presented in thi study (ect on II 4 and III 6)

The re ults obtained when surveying the incidence of EBN in AC county in thi way are presented in Fig 10 (page 42)

Fig 9 Mean prevalence of EBN December 1959 - April 1974 for the 12 municipal districts of AC county and for the inland and the coastal region (figure below the name of the district/region); number of cases per 1 000 inhabitants and year. Above the name of each district/region is given the ratio of its mean prevalence to that of the county s Boundaries between municipal districts - - - and between inland and coastal regions — — —

Fig 10 Incidence of EBN in AC county for 16 consecutive seasons lasting from May one year to the following April
For designation of cycles cf the text

III 5 Incidence of EBN

III 5 1 Monthly incidence

Table XI (page 44) shows the incidence (nos of cases registered) of EBN in AC county for the period 1959 - 1975

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Cases of EBN were diagnosed for every year of the period studied but in a varying number ranging from two cases in 1959 and 1968 to 92 in 1974

III 5 4 Seasonal incidence

Subsequently th incidence of EBN in AC county was studied for seasons each lasting from May one year to the follow ing April i e for periods identical to those for which information on prevalence of mall rodents in northern Sweden was p esented in this tudy (section II 4 and III 6)

The results obtained when surveying the incidence of EBN in AC county in this way are p esented in Fig 10 (page 42)

Table XI Monthly incidence of EBN in AC county Sweden; 1959 to 1975

Month	Year 1959	-60	-61	-62	-63	-64	-65	-66	-67	-68	-69	-70	-71	-72	-73	-74	-75	Total for month	Total for quarter
Jan		1	2					1			2	3			5	14	1	29	
Feb			1								1		1		2	7		12	
March			1			2			2		1	1			4	7	1	19	60
April				1		1		1	1		1	1	1		2	3		12	
May					2	1			1			1			4	5		14	
June								1	1			2			3	3		10	36
July					3	1	1	4	2		1	4			4	19	1	40	
Aug			2	2	3			3	1		1	8		1	4	12	1	38	
Sept	1			1	2			2			1	2	2		8	4	1	24	102
Oct		1			1	1		8		1	7	2	1	1	10	7		40	
Nov		2		6	2		2	7		1		3	1	1	17	5		47	
Dec	1	5		2	3	1	4	3	1		6		2	1	14	6		49	136
Total	2	9	6	12	16	7	7	30	9	2	21	27	8	4	77	92	5	334	334

Subsequently any numerical difference in number of cases between seasons was rated as representing an interseasonal variation in the incidence of the disease The main arguments for adopting this view were as follows

(a) The clinical records among which cases of EBN were sought were collected from the files of the three hospitals to which were referred for the period studied members of the entire county population in need of hospital care

(b) Subdividing the period examined into sections lasting from May one year to the following April does not alter the orderly sequence in which the cases were registered; therefore no obvious reason was found to assume that this procedure would appreciably influence the findings presented in section III 5 1 of this study viz a very low probability for the variation in number of cases of EBN being the consequence of chance variation

(c) S gnificant differences were found between the distributions of case of EBN for seasons with a separate grade of prevalence of small rodents (low middle high or very high); cf section III 7 3 page 51

The number of cases was found to increase for two to four con ecutive seasons after which it dropped to rise again (Fig 10 page 42); th s was the case for patients living outside (except for 1968/69) as well as inside built-up areas (except fo 1963/64) Starting when a minimized incidence of EBN was recorded i e in the seasons of 1961/62 64/65 67/68 and that of 1971/72 the time interval studied covers five periods during which the asonal incidence of EBN in AC county shifts in imila fa hion first rising and then falling

To t st for the presence of any periodicity among the set of umber repres nting the seasonal incidence of EBN as ob r d in AC county the interseasonal chang s in number of case we e compared at intervals of increasing length This was do e in the following way The set of numbers representing the s sonal incidence of the disease was repeated below itself starting one (two three 14) season(s) after the first on examined The change in number of cases between seasons (an increase or a decre se) was indicated separately in each row of number using arrows (cf Fig 11 page 50) The congruence of

Table XI Monthly incidence of EBN in AC county Sweden; 1959 to 1975

Month	Year 1959	-60	-61	-62	-63	-64	-65	-66	-67	-68	-69	-70	-71	-72	-73	-74	-75	Total for month	Total for quarter
Jan		1	2					1			2	3			5	14	1	29	
Feb			1								1		1		2	7		12	
March			1			2			2		1	1			4	7	1	19	60
April				1		1		1	1		1	1	1		2	3		12	
May					2	1			1			1			4	5		14	
June								1	1			2			3	3		10	36
July					3	1	1	4	2		1	4			4	19	1	40	
Aug			2	2	3			3	1		1	8		1	4	12	1	38	
Sept	1			1	2			2			1	2	2		8	4	1	24	102
Oct		1			1	1		8		1	7	2	1	1	10	7		40	
Nov		2		6	2		2	7		1		3	1	1	17	5		47	
Dec	1	5		2	3	1	4	3	1		6		2	1	14	6		49	136
Total	2	9	6	12	16	7	7	30	9	2	21	27	8	4	77	92	5	334	334

cycles (O - Q) two (O P) consisting of three and one (Q) of four seasons The period studied ends with a cycle R composed of at least three seasons Whether season 1974/75 constitutes the end of cycle R or the beginning of a new cycle (S) can not be decided yet

From the season with the lowest incidence of EBH starting one cycle to the one with the highest incidence ending that cycle the mean number of cases rose 8 9 times (range 4 0-15 8) Cases of EBH were diagnosed for each of the 16 seasons covered in this study and in a rising number; during the first eight seasons 92 and during the eight last ones 239 cases were diagnosed a more than twofold increase Also for seasons when a minimized incidence of EBH was recorded the number of cases doubled from three for season 1959/60 and 1961/62 to six for season 1967/68 and that of 1971/72

III 6 Seasonal prevalence of small rodents in northern Sweden

Table XII (page 48) presents information on the seasonal pr valence of small rodents in northern Sweden including AC county for the period 1959 1975 as reported by zoologists (section II 4 2) When summarizing the ratings of different observers information on the seasonal prevalence of animals was obtained for every season of the period studied

For 13 of the 16 seasons studied numerical information was available in the form of catch statistic (14 16 22) or the extent to which rodents were found in stomachs of the red fox (10) indicating the change (increase or decrease) taking place between seasons in amount of small rodents captured or consumed a prey When matching fo individual seasons the numerical information available to the ratings of the small rodent prevalence presented an increase in the amount of animals between easons was found to correspond to a rating of the prevalence a middle or high/very high (peak) and a decrease to a rating of the prevalence as low (Table XII page 48)

When examining the season sequentially the prevalence of small rodents was found to in rease for a period of two and in one instance three consecutive easons to reach high or very high levels during the following third or fourth season This

changes in seasonal incidence of the disease was studied between rows by comparing to what extent corresponding arrows pointed in the same direction This was done for each position of the two sets of numbers relative to each other obtained when increasing the distance between the opening seasons one season at a time The results were tested statistically from the first to the ninth position applying a one-sided hypothesis and using a sign test (51)

When the interval between the sets of numbers amounted to three seasons (Fig 11 page 50) the interseasonal change in number of cases was found to coincide in 10 out of 12 instances where comparison between rows was possible; this result was significant when tested statistically (p < 0 019) For other positions i e a distance between opening seasons shorter or longer than three seasons the interseasonal changes in number of cases did not coincide to such an extent that significant results were obtained when statistically testing them; for distances longer than nine seasons the number of occasions when comparison between rows was possible diminished to such low numbers that statistical analysis using a sign test became inapplicable These results were interpreted as follows

When registered for periods from May one year to the following April the seasonal incidence of EBN in AC county was found to vary with such regular periodicity that its designation as a cyclical event was found appropriate A successive increase in number of cases for three consecutive seasons was found to be the most common event; only one complete four-year cycle was observed

A cyclical fluctuation in the seasonal incidence of the disease with a period of usually three but also four years was thus found to be a characteristic of EBN for the period and area studied

Those seasons forming the interval between periods when a minimized number of cases of EBN was recorded are hereafter called a cycle and each of these intervals is designated with a letter (N - R) The period examined in this study starts with a period N (season 1959/60 and that of 1960/61) that probably constitutes the end of such a cycle Then follow three complete

cycles (O - Q) two (O P) consisting of three and one (Q) of four seasons The period studied ends with a cycle R composed of at least three seasons Whether season 1974/75 constitutes the end of cycle R or the beginning of a new cycle (S) can not be decided yet

From the season with the lowest incidence of EBN starting one cycle to the one with the highest incidence ending that cycle the mean number of cases rose 8 9 times (range 4 0-15 8) cases of EBN were diagnosed for each of the 16 seasons covered in this study and in a rising number; during the first eight seasons 92 and during the eight last ones 239 cases were diagnosed a more than twofold increase Also for seasons when a minimized in idence of EBN was recorded the number of cases doubled from three for season 1959/60 and 1961/62 to six for season 1967/68 and that of 1971/72

III 6 Seasonal prevalence of small rodents in northern Sweden

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When examining the seasons sequentially the prevalence of small rodents w s found to increase for a period of two and in one instance three consecutive seasons to reach high or very high levels during the following third or fourth season This

Table XII Seasonal prevalence from May to the following April of small rodents in northern Sweden including AC county; spring 1959 to 1975 Information cumulated from six different sources
Underlined letters indicate seasons when numerical information is available - in the form of catch statistics (14 16 22) or the extent to which rodents were found in stomachs of the red fox (10)
Ratings of the seasonal prevalence is presented verbally: L - a low M - a middle P - population peak equivalent to H - a high or VH - a very high prevalence of animals
Numerical information (10 14 16 22) is presented as the change in the variable studied taking place between seasons I - increase D - decrease compared with adjacent seasons | Beginning (and end) of an evolutionary cycle of small rodents (N - R); cf the text

Season and corresponding prevalence of small rodents

Reference	1959/60	60/61	61/62	62/63	63/64	64/65	65/66	66/67	67/68	68/69	69/70	70/71	71/72	72/73	73/74	74/75
(16)	M	P	L	M	P	L	I/M	I/P VH	D/L	I						
(17)		P			P			P			P	P			P	
(10)		I	D						D	I	I					
(26)		P	L	M	P	L		P	L		P	P				
(27)		P			P			P			P	P			P	
(14)										I	I					
(58)						L	M	VH	L	M	H	H	L	M	VH	
(22)														I	I	D
Cumulated information	M	H	L	M	H	L	M	VH	L	M	H	H	L	M	VH	L
Cycle	N			O			P			Q				R		

sequence of events was repeated five times during the period studied and such a sequence is hereafter referred to as an evolutionary cycle of small rodents each of which is designated with a letter (N – R)

The period studied starts with two seasons (1959/60 and 1960/61) that possibly represent the conclusion of an evolutionary cycle of small rodents (N) Then follow two cycles (O P) consisting of three seasons each and one cycle (Q) composed of four seasons The period studied ends with a season (1974/75) that might either form the end of cycle R or the beginning of another (S); the probability that it will form part of a five-year cycle can not be excluded however

III 7 Comparison between the incidence of EBM in AC county and the prevalence of small rodents in northern Sweden

III 7 1 Seasonal variations

In Fig 12 (page 50) variations in seasonal incidence of EBM in AC county (section III 5 4) were compared to correspondent changes in prevalence of small rodents in northern Sweden (section III 6) using arrow to indicate the change (a rise or fall) that took place between consecutive seasons in number of cases and in quantity of animals respectively

Using thi method of comparison congruence was found for at least 14 and pos ibly 15 seasons in succession between interse sonal changes in prevalence of small rodents in northern Sweden and analogous variations in seasonal incidence of EBM in AC county which forms part of that territory The probability that this outcome might be the consequence of chance va iation is small ($p < 0$ 001 using a sign test); the confidence of thi result is influenced however i e by the circumstance that fo three of the seasons studied information on the prevalence of small rodents in northern Sweden was obtained olely as atings

Table XII Seasonal prevalence *from May* to the *following April of* small rodents in northern Sweden including AC county; spring 1959 to 1975 Information cumulated from six different sources
Underlined letters indicate seasons when numerical information is available - *in* the form of catch statistics (14 16 22) or the extent to which rodents were found in stomachs of the red fox (10)
Ratings of the seasonal prevalence is presented verbally: L - a low M - a middle P - population peak equivalent to H - a high or VH - a very high prevalence of animals
Numerical information (10 14 16 22) is presented as the change in the variable studied taking place between seasons: I - increase D - decrease compared with adjacent seasons | Beginning (and end) of an evolutionary cycle of small rodents (N - R); cf the text

Reference	1959/60	60/61	61/62	62/63	63/64	64/65	65/66	66/67	67/68	68/69	69/70	70/71	71/72	72/73	73/74	74/75
(16)	M	P	L	M	P	L	I/M	I/P VH	D/L	I						
(17)		P			P			P			P	P			P	
(10)		I	D						D	I	I					
(26)		P	L	M	P	L		P	L		P	P				
(27)		P			P			P			P	P			P	
(14)										I	I					
(58)																
(22)						L	M	VH	L	M	H	H	L	M	VH	
Cumulated information														I	I	D
	<u>M</u>	<u>H</u>	<u>L</u>	M	H	<u>L</u>	<u>M</u>	<u>VH</u>	<u>L</u>	<u>M</u>	<u>H</u>	H	<u>L</u>	<u>M</u>	<u>VH</u>	<u>L</u>
Cycle	N			O			P			Q				R		

III 7 3 Seasonal accumulation of cases

The registered interseasonal differences in number of cases of EBN were analyzed by summarizing the monthly number of cases separately for seasons (May - April) with a different grade of small rodent prevalence (low middle high or very high) The monthly totals obtained were then cumulated and the proportion each of them amounted to of the seasonal total was calculated Three cumulative frequency distributions at intervals of one month were thus obtained one for each type of season studied (cf Fig 18 page 55) The monthly proportions were then subtracted and the numerically largest difference (D) obtained was studied A two-sided hypothesis was tested and applying KOLMOGOROV SMIRNOV s two-sample test (51) the three differences studied were all found to be significant (Table XIII)

Table XIII Monthly proportion of cases of EBN registered in AC county for seasons (May April) with a separate grade of prevalence of small rodents in northern Sweden: (L) low (M) middle (H) high or very high; (D) maximum differ n e between cumulated distributions A two-sided hypothesis was tested using KOLMOGOROV SMIRNOV's two-sample test P value denotes the probability that the two distributions compared have been drawn from the same population or from populations with the same distribution (Cf also Fig 18 page 55)

Se sons compared	D_{max} of $S_{n1}(X)$ $S_{n2}(X)$	Statistic	P
S_{62} (L) - S_{47} (M)	0 598	0 358	< 0 001
S_{62} (L) S_{202}(H)	0 347	0 255	0 001
S_{202}(H) S_{47} (M)	0 285	0 280	< 0 005

III 7 2 Cyclic variations

The seasonal changes in prevalence of animals characteristic of an evolutionary cycle of small rodents consist in a successive rise in quantity of animals terminated by a (usually) *sharp fall in their number (section II 4) The seasonal incidence* of EBN in AC county varied in a similar fashion (section III 5 4) These cyclic variations in seasonal incidence of EBN in AC county northern Sweden were found for the period studied to occur simultaneously and in phase with the cyclic variations in the seasonal prevalence of small rodents taking place in that area (section III 6)

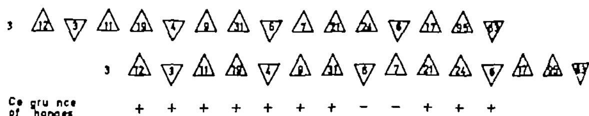


Fig 11 Consecutive interseasonal (May to following April) changes (△ increase ▽ decrease) in registered number of cases of EBN (figures within arrows) in AC county 1959 - 1975 compared at an interval of three seasons (cf the text) Interseasonal changes between rows (direction of correspondent arrows) concordant: + discordant: - P < 0 019 (sign test)

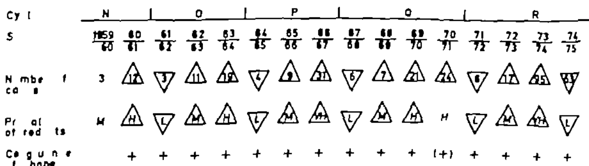


Fig 12 Consecutive interseasonal (May to following April) changes (△ increase ▽ decrease) in number of cases of EBN observed in AC county 1959 - 1975 matched to changes in prevalence of small rodents in the area for correspondent periods Beginning (and end) of cycles (N - R) is indicated Interseasonal changes between rows (direction of correspondent arrows) concordant: + possibly concordant (+) P < 0 001 *(sign test)*

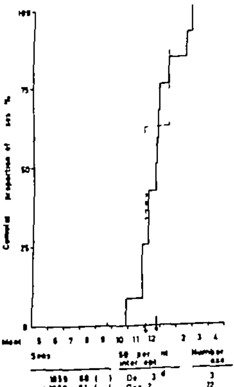


Fig 13
Cycle N

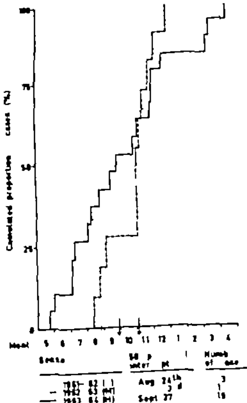


Fig 14
Cycle O

Fig, 13-18 Cumulated proportions of cases of EHN diagnosed in AC county during seasons with
operate grade of prevalence of small rodents in northern Sweden: (L) low (M) middle (H)
high or (VH) very high The distributions obtained for seasons composing one evolutionary
cycle of small rodents are displayed together on a common time scale The projection on the
time scale of the 50th percentile intercept of each distribution examined is indicated with
an arrow and the date thus obtained is given for each season studied

The very low probability that the differences analyzed might be the consequence of chance variation strongly supports the conclusion that the number of cases of EBN registered during seasons with a separate grade of prevalence of small rodents form distributions differing with respect to each other

The distribution of cases of EBN for seasons with a separate grade of prevalence of small rodents are drawn in Figs 13-17 and summarized in Fig 18 pages 53-55 To obtain these distributions the registered number of cases were summarized at three-day intervals and cumulated separately for each season studied on a time scale common to those seasons composing one evolutionary cycle of small rodents The projection on the time scale of the 50th percentile intercept was recorded separately for each season studied

When read as the intercept with the 50th percentile the mean interval between distributions obtained for seasons with a low and the following ones with a middle prevalence of small rodents was four months (range 2 3-5 6) The distributions obtained for seasons when the prevalence of small rodents was of a high or very high grade fell somewhere in between those obtained for the other seasons of the cycle when the prevalence of animals was of a different grade (low or middle) This was also the case for cycle Q (Fig 16 page 54) consisting of two seasons with a prevalence of small rodents of a high grade in succession (that of 1969/70 and 1970/71)

The mean interval between seasons with a middle and those with a high or very high prevalence of small rodents was 1 5 months (range 0 7-2 4) when read as the intercept with the 50th percentile

77 per cent of the cases of EBN diagnosed when the prevalence of small rodents was of a low grade were registered during the first half (May - October) of these seasons When the prevalence of small rodents was of a middle grade the corresponding figure was 17 per cent and when the prevalence was of a high or very high grade it was 46 per cent

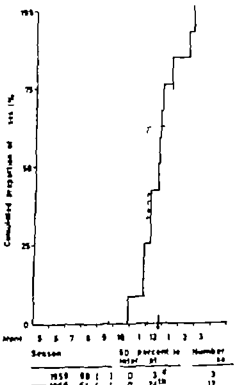


Fig 13
Cycle N

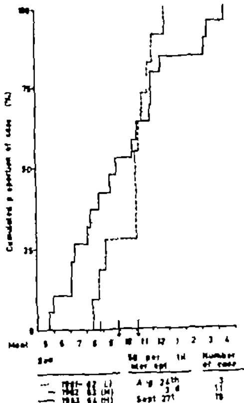


Fig 14
Cycle O

Fig 13 18 Cumulated proportions of cases of EBN diagnosed in AC county during seasons with s parate grades of prevalence of small rodents in northern Sweden: (L) low (M) middle (H) high or (VH) very high The distributions obtained for seasons composing one evolutionary cycle of small rodents are displayed together on a common time scale The projection on the time scale of the 50th percentile intercept of each distribution examined is indicated with an arrow and the date thus obtained is given for each season studied

The very low probability that the differences analyzed might be the consequence of chance variation strongly supports the conclusion that the number of cases of EBN registered during seasons with a separate grade of prevalence of small rodents form distributions differing with respect to each other

The distribution of cases of EBN for seasons with a separate grade of prevalence of small rodents are drawn in Figs 13-17 and summarized in Fig 18 pages 53-55 To obtain these distributions the registered number of cases were summarized at three-day intervals and cumulated separately for each season studied on a time scale common to those seasons composing one evolutionary cycle of small rodents The projection on the time scale of the 50th percentile intercept was recorded separately for each season studied

When read as the intercept with the 50th percentile the mean interval between distributions obtained for seasons with a low and the following ones with a middle prevalence of small rodents was four months (range 2 3-5 6) The distributions obtained for seasons when the prevalence of small rodents was of a high or very high grade fell somewhere in between those obtained for the other seasons of the cycle when the prevalence of animals was of a different grade (low or middle) This was also the case for cycle Q (Fig 16 page 54) consisting of two seasons with a prevalence of small rodents of a high grade in succession (that of 1969/70 and 1970/71)

The mean interval between seasons with a middle and those with a high or very high prevalence of small rodents was 1 5 months (range 0 7-2 4) when read as the intercept with the 50th percentile

77 per cent of the cases of EBN diagnosed when the prevalence of small rodents was of a low grade were registered during the first half (May - October) of these seasons When the prevalence of small rodents was of a middle grade the corresponding figure was 17 per cent and when the prevalence was of a high or very high grade it was 46 per cent

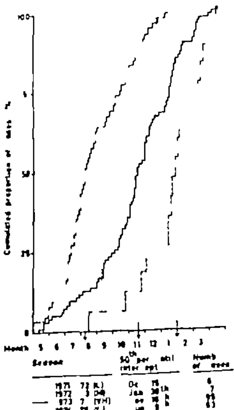


Fig 17
Cyclo R

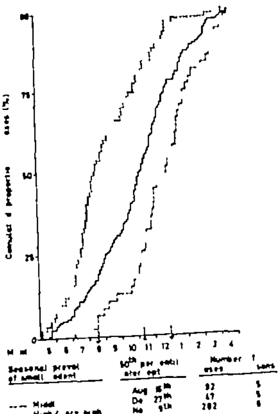


Fig 18
Composite picture showing the mean distributio
for all cases of EBN diagnosed for seasons wit
a separate grade of prevalence of small rodent
during the period studied

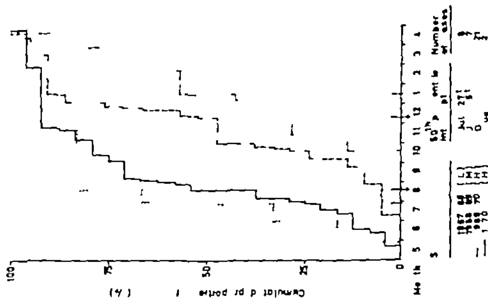


Fig 16
Cycle Q

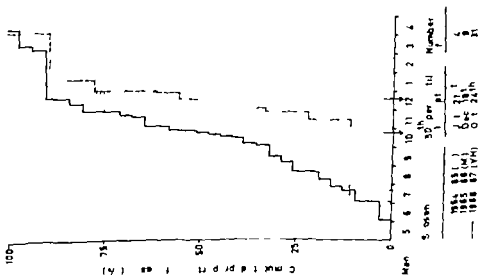


Fig 15
Cycle P

(e) A three-year cycle is thus terminated by three seasonal halves in succession (the second half of the season with a middle and the two halves of the season with a high or very high prevalence of small rodents) i e a period of one year and a half characterized by an augmented incidence of EBN; 73 per cent (n = 241) of the total number of cases of EBN diagnosed during the period examined in this study were registered in that interval

(f) 19 per cent (n = 63) of the total number of cases of EBN diagnosed during the period examined in this study were registered during the first half of seasons when the prevalence of small rodents was rated as low

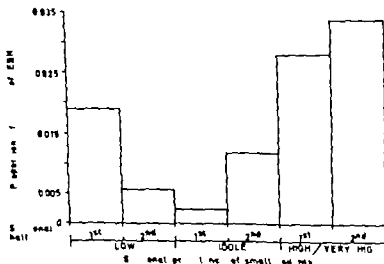


Fig 19 Proportion of cases of EBN registered in AC county for first (May October) and second (November - April) halves of season with a separate grade of prevalence of small rodents in northern Sweden: low middle high or very high

III 8 Incidence of EBN in relation to meteorological variable

The actual values of the meteorological data collected wer studied as well as their relative change between different yea s and for va ious intervals (months periods of the year) No con iat nt co gruence could be discerned when the meteorological data were matched with the corresponding incidence of EBN; therefor the analysis was not carried ...

III 7 4 Survey of incidence of EBN in relation to preva lence of small rodents

When related to the changes in abundance of small rodents observed in northern Sweden the seasonal incidence of EBN in AC county was found to vary in a cyclical fashion with a peri odicity of three to four years (section III 5 4) Within each cycle the following characteristics were observed regarding the appearance of cases of EBN (Fig 19 page 57)

(a) For seasons opening the cycle when the amount of small rodents was decreasing i e when the prevalence of animals was rated as low when compared with adjacent seasons the number of cases of EBN also decreased and the majority of cases diagnosed were registered during the first half (May - October) of these seasons

(b) For seasons when the amount of small rodents increased to reach an abundance rated as lying between that of the pre ceding and the following season(s) i e for seasons with a middle prevalence of small rodents the number of cases of EBN also increased to a level above that of the preceding season but not reaching the level of the following season and the majority of the cases diagnosed were then registered during the second half (November - April) of these seasons

(c) This accumulation of cases of EBN to the first season al half for seasons opening a cycle immediately followed by a season when the cases accumulate during the second seasonal half leaves a period of one year extending approximately from low-seasonal November to the following middle-seasonal October when comparatively few cases of EBN were observed; only eight per cent (n = 27) of the total number of cases diagnosed during the period examined in this study was registered in that inter val

(d) For seasons when the amount of small rodents rose to the highest level during the cycle i e during seasons closing the cycle with a high or very high prevalence of small rodents the maximum number of cases of EBN was also reached and the cases were fairly evenly distributed over the two halves of these seasons

clinical entity separable from other conditions with an acute onset and accompanied by signs of kidney affection; this view was also adopted in this study Probably subclinical cases exist however where the disease runs a course mild enough not to force the patients to seek medical advice

All patients matching the applied criteria were accepted as cases of EBN; only a few probably less than ten were found who had an original diagnosis other than epidemic nephropathy or EBN The day of falling ill was estimated for all cases without difficulty

Although care was taken to apply the diagnostic criteria uniformly throughout the whole study the probability remains of erroneous decisions having been made when assessing the information obtained from the clinical records Moreover cases of EBN might also have been missed i e because the bulk of the record examined had to be kept within reasonable limits The magnitude of the error thus introduced into this study cannot be e timated w th certainty but is rated to be small enough not to influence appreciably the main results presented; one reason for this conclusion is the cyclic variation demonstrated for the easonal incidence of the disease

The incubation time of EBN and its mode of transmission till being undetermined no effort was made in thi study to seek information on the patients activities prior to contracting the di ease The majority of patients reported having been at home when the r illne s began and therefore the sites of thei domiciles were examined when studying the prevalence of the disease

IV 2 Distribution of cases among different sections of the county population

51 1 per cent of the mean population in AC county for the period studied onsisted of males Among these 77 5 per cent of the c ses of EBN were diagnosed a proportion close to that reported from Finland 80 3 per cent (29) but lower than that obtained in a previous investigation carried out in AC county (45) where 89 9 per cent of the patients were men

In this study the male predominance was demonstrated for

IV DISCUSSION

IV 1 Design of the present study

The present study was limited to AC county the area estimated to be sufficiently large for cases of EBN if any to be encountered even during years with very low incidence of the disease

January 1959 was chosen as the starting point because clinical records written before that date generally were rated as containing an insufficient amount of information to meet the standards set up for this study The period thus covered was estimated to be of a length sufficient to yield enough material to fulfil the purpose of this study

The discriminating characteristics applied in this study when documenting cases of EBN were set up using information from papers on epidemic nephropathy containing i a many detailed casuistical reports; in addition personal experience had been gained of cases seen at Umeå University hospital; the criteria had to be applicable also to records written in county hospitals using standard diagnostic procedures (Skellefteå and Lycksele)

The case histories obtained were all quite similar and in essence identical with those repeatedly summarized in the literature on epidemic nephropathy Characteristically the patients were suddenly taken ill with a rapidly rising body temperature for which no obvious cause could be demonstrated The condition was accompanied by a distressing ache and pain mostly in the back and in the abdomen to which was added lack of appetite nausea vomiting obstipation and a feeling of fullness; sometimes however diarrhoea was present Proteinuria and elevated concentration of serum non protein nitrogen were found in almost all cases studied The disease was self-limiting; full recovery was the rule and the course was uneventful for all cases examined in this study

In spite of the repeated inability to demonstrate an etiologic agent capable of generating the symptoms and signs in these patients most observers agree that the disease is a

clinical entity separable from other conditions with an acute onset and accompanied by signs of kidney affection; this view was also adopted in this study Probably subclinical cases exist however where the disease runs a course mild enough not to force the patients to seek medical advice

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In this tudy the male predominance was demonstrated for all age-groups [illegible]

IV DISCUSSION

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from AC county (45 47) where 66 7 per cent of the cases were of that age but lower than the proportion reported in a Norwegian study (61) 78 6 per cent In a study covering the whole of Finland (29) 57 8 per cent of the cases were found among people aged 20-40 years

Seven of the patients were 15 years or younger This proportion 2 6 per cent is the lowest reported among children In a study from Norway (61) 3 6 per cent of the cases were children and the corresponding proportion in previous studies carried out in AC county was 5 5 per cent (45) and 11 5 per cent (47) respectively In a Finnish study (29) the overall proportion of children was 5 7 per cent but in the south-eastern part of the country it was as high as 13 per cent being the highest reported proportion of cases among non-adults The low proportion of children among the cases of EBN examined in this study could not be satisfactorily explained but the children were not studied separately mainly because of the few cases diagnosed among them No pediatric study on cases of EBN has hitherto been published and as the diagnostic criteria applied in this tudy we e chosen from findings made in adults they are possibly not directly applicable to children

IV 3 Changes in geographic distribution of county population for the per od tudied

For years other than 1960 1965 and 1970 when a census was arried out the numbe of people living outside and inside built-up area respectively (Table III V pages 19 21 and 23 respectively) had to be calculated This wa done linearly as the number of people inhabiting the sparsely populated area of the county was found to decrease at an almost constant r te whether studied for the nland or fo the coastal region

IV 4 Prevalence of EBN in areas of different population density

For the period studied a significantly higher prevalence of EBN (number of cases per 1 000 inhabitants and year) was found among that part of the county population inhabiting the sparsely populated area than among those living in the built-up rea (section III 1) The g dual decline during the period

ulated area of the county and for those living in the built-up areas as well females 65 years or older in built-up areas being an exception A satisfactory explanation for this male predominance among people diagnosed as cases of EBN could not be found in this study Assuming EBN to be of an infectious origin a difference in susceptibility to the infectious agent might be assumed to exist between the sexes males being more sensitive to it than females

A difference between the sexes in maximum serum creatinine concentration and in age similar to that demonstrated in this study was found among 12 patients from Norway (31) Two-thirds of these cases were men with a mean age of 36 years and a mean maximum serum creatinine concentration of 5 8 mg per 100 ml The corresponding figures for the female cases were 46 years and 6 9 mg per 100 ml respectively No explanation was found in this study for these differences in maximum serum creatinine concentration between the sexes

The occupational survey presented in Table X (page 31) indicates that cases of EBN were diagnosed among people of very different professions and among different social classes of the community Previous reports from Sweden in 1963 (45) and Norway in 1954 (61) that the majority of the cases with nephropathy were to be found among certain occupational classes mostly farmers and/or lumberers were not substantiated by the results of this study The report from Finland in 1971 (29) that 70 per cent of the patients were farmers or members of farm families could not be verified among the cases from AC county

The number of people occupied in forestry and farming has declined substantially in Sweden during the last decade a fact that might explain partly the different proportions of cases among lumberers and farmers reported at different times and from different Scandinavian countries

The morbidity caused by EBN among people occupied in medical service was not raised (section III 2 3) and no evidence was found that they had fallen ill as a consequence of attending cases of the disease

71 5 per cent of the cases were aged 20-40 years a proportion slightly higher than that reported in previous studies

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IV 4 Prevalence of EBH in areas of different population density

For the period studied a significantly higher prevalence of EBH (number of c s s per 1 000 inhabitants and year) was found among that part of the county population inhabiting the sparsely populated area than among those living in the built-up areas (section III 1) The gradual decline during the period

studied in number of people living outside the built-up areas of the county was not accompanied by a proportionate lowering of the prevalence among that part of the county population nor by a proportionate increase in prevalence among the steadily growing population of the built-up areas; the prevalence of EBN continued to be higher among people living outside built-up areas than among those living inside these areas for the whole period studied Consequently the relation in prevalence between the areas differing with respect to population density remained unaltered in spite of the substantial shift of the county population taking place during the period studied

The prevalence of EBN was also significantly higher among the inhabitants of the thinly populated inland region than among people inhabiting the more densely populated coastal region

Cases of EBN occurring among town-dwellers are mentioned only in passing by previous investigators (29) which may convey the impression that they might be rare Such a view was not supported by the results of this study 18 7 per cent of the cases being diagnosed among town-dwellers

Between people living outside and those living inside built-up areas of the county no difference was found in the distribution of population or of cases according to sex and age-groups sufficiently large to explain the higher mean prevalence of EBN among that part of the county population living outside built-up areas

No reason was found in this study to assume differences in hygienic conditions standard of living or food habits to exist between the county population living inside and that living outside the built-up areas of a magnitude sufficient to cause discernible differences in susceptibility to a supposed infectious agent Moreover assuming the prevalence of EBN to be appreciably influenced by such factors then the advance in social welfare made during the period covered by this study would most likely have resulted in a drop in the prevalence of the disease which was not the case The prevalence of the disease was instead found to increase during the period studied and the highest prevalence registered in this study was for the last season examined in detail that of 1973/74

Sometimes the view is expressed that people living in rural surroundings or far from community centres seek medical advice proportionately less often than do people inhabiting built up areas Such a mechanism might have been at work in the mat rial examined in this study but its effect would then have been to diminish the proportion of cases diagnosed among that part of the population living outside built up areas Therefore such a mechanism could not explain the higher prevalence found among people living in the sparsely populated area of the county

Using the maximum serum creatinine concentration registered during the acute phase of the disease as a measure of the severity of the kidney affection sustained no significant difference was found when comparing the means for males living outside and inside built up areas nor for females inhabiting corresponding areas Differences in the severity of the kidney reaction therefore did not explain the differences in prevalence of EBN found in this study between the county population l ving outside and inside built-up areas

In this section are discussed those results of the present study that demonstrate a ignificantly higher prevalence of EBN to be present among people in AC county living more distantly apart than among those living more closely grouped using the concept population density in two different ways population of the sparsely populated area of the county versus that of the built up areas and population of the thinly populated inland region ve sus that of the more densely populated coastal region These results may convey the impre sion that an inverted relationship exists between the population density of AC county and the prevalence of EBN in that area; they might possibly be ex plained by assuming the existance of a contagious factor more prev iling outside than inside those parts of the county where people live closely g ouped (towns and built up areas)

IV 5 Geographic distribution of cases

Cases of EBN diagnosed in AC county during the separate seasons examined in this study were found to vary considerably in number and also to appear within areas of very different sizes ranging from two of the 12 municipal districts of the county to the entire area studied (section III 4)

When observing the order in which the cases appeared and surveying the geographic positions of their domiciles relative to each other no definite starting point(s) for the (seasonal) outbreaks of the disease could be discerned within the area(s) examined Especially during seasons when many cases of EBN were diagnosed it was evident that within a brief period they appeared in places widely apart and no evidence was obtained indicating that the disease was propagated from one place within AC county to another Neither could any contact between the cases be demonstrated the four instances where two and three members of the same families respectively contracted the disease within a short interval being an exception probably without real significance as they all occurred within the sparsely populated area of the county where the major proportion of the cases contracted the disease

When calculating the mean yearly prevalence for the whole period studied separately for each municipal district a figure equivalent to or higher than the county mean was obtained for those districts situated in the central and northern parts of the county and in the eastern parts of the inland region while the corresponding figure for the remaining parts of the county was below that of the county mean The longitudinal difference between municipal districts of AC county in mean prevalence of cases of EBN for the period studied might possibly be a consequence of the tendency of field populations of small rodents to fluctuate with an augmented amplitude on more northerly latitudes than on more southerly ones (section II 4 1 c) No explanation was found in this study for the difference observed in mean prevalence of EBN between eastern and western municipal districts of the inland region of AC county

IV 6 The endemic nature of the disease

In the area(s) examined and for the period studied no evidence could be demonstrated in favour of EBN a being of an epidemic nature in the sense of a (contagious) disease that might spread over large areas usually then affecting a considerable proportion of the population From a nosographic and epidemiologic point of view the disease studied here is therefore better characterized as being of an endemic nature The main arguments for this opinion are:

(a) cases appeared anywhere in the area studied

(b) cases were diagnosed every year during the period examined

(c) the low prevalence

(d) no evidence was obtained in favour of the disease being propagated from person to person

IV 7 Incidence of EBN in AC county

Cases of EBN were diagnosed in the area examined for every season studied The seasonal incidence of the disease was found to change in a cyclical fashion although with variations in amplitude No clue to the cause of these variations was found when examining the individual case histories neither were any variations found similar to those recorded for the seasonal incidence of EBN when studying the climatic conditions prevailing in the a ea during the period covered by this study

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IV 9 Associations between the incidence of EBM and the prevalence of small rodents

In this study the relationship between the incidence of EBM as observed in AC county and the prevalence of small rodents in northern Sweden was examined in different ways

(a) A close correspondence was found between the seasonal and cyclic variations of the two phenomena (section III 7 1 - 2)

(b) Chance was found to be an unlikely explanation for the variations observed in the incidence of the disease (section III 5 1) and when comparing the number of cases diagnosed during seasons with a separate grade of prevalence of small rodents the distributions obtained were found to differ significantly (section III 7 3)

(c) The findings in (b) were illustrated by the graphic pictures obtained when plotting the cumulated proportions of number of cases on a time scale common to seasons composing evolutionary cycles of small rodents (Figs 13-18 pages 53-55); the distributions for seasons differing with respect to prevalence of small rodents were found to run more or less spaced and to reach the 50th percentile at different times of the season(s)

(d) Also the proportion of cases diagnosed during first and second halves of seasons with a separate grade of prevalence of small rodents was found to differ (section III 7 4 ; Fig 19 page 57)

A tentative explanation for the findings in (c) and (d) might be found when relating them to changes in number of animal char cte istic of an evolutionary cycle of small rodents (1 35)

During the first and possibly also during the second half of seasons opening an evolutionary cycle of small rodents the number of animals declines to (very) low numbers The intercept with the 50th percentile for distributions obtained when cumulating the proportion of cases of EBM diagnosed during these easons fell on an average in the ~~beginning~~ middle of ~~September~~ August, i e in the first seasonal half during which 19 per cent of the total seasonal number of cases studied (n = 331) were registered

IV 8 Information on prevalence of small rodents in northern Sweden

The validity of the general outline of small rodent field population dynamics accounted for in section II 4 1 of this study will not be discussed in this presentation the topic being covered in literature on ecological zoology Likewise no attempt was made to appraise the reliability of each individual observer s ratings of the prevalence of small rodents including the numerical information presented Most observers referred to in this study use verbal descriptions when reporting the prevalence of small rodents Using information of this kind in the manner adopted in this study (section III 7) will invariably introduce a factor of uncertainty The circumstance however that the majority of individual observers report similar estimations of the seasonal prevalence of small rodents in northern Sweden confers upon the information obtained a degree of reliability rated as sufficient for the purpose of this study

One of the consequences of describing the seasonal prevalence of small rodents verbally is that the terms used recur in an identical order within each evolutionary cycle examined Although repeated in this way (low middle high or very high - peak) verbally identical terms must not be interpreted as standing for an always identical quantity of small rodents; they are used expressly with the intent of characterizing the actual seasonal prevalence of animals compared to that of adjacent seasons Consequently they also indicate the change in quantity of animals estimated to have taken place between seasons (an increase or a decrease) except for seasons rated as having a similar prevalence of small rodents (that of 1969/70 and 1970/71)

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I am very much indebted to R Toft for his generous assistnce throughout this study His readine s whenever I felt the need to discuss at length details of the ecological a pects of this tudy has been inspiring and a gre t comfort to me when venturing into the domains of ecological zoologists My thanks ar also extended to H Hansson and B Börnfelt for supplying me with information on the prevalence of small rodents to

while the corresponding figure for the second seasonal half was six per cent

During the following season of the evolutionary cycle of small rodents the number of animals increases, also during (part of?) its second half and for these seasons the intercept with the 50th percentile fell on an average at the end of December i e in the second seasonal half for which 12 per cent of the total number of cases studied were observed During the first seasonal half the corresponding figure was only two per cent the minimum proportion of cases registered for seasonal halves of the small rodent evolutionary cycle

During seasons closing the cycle the number of animals continues to increase at least during the first half of these seasons to reach maximum levels during the cycle For these seasons the intercept with the 50th percentile fell on an average in the beginning of November i e shortly after mid-season (October 31st) During the first half of these seasons 28 per cent of the total number of cases were registered and during the second half 33 per cent the latter figure being the maximum proportion of cases registered for seasonal halves of the small rodent evolutionary cycle

These findings were interpreted as being in favour of an intraseasonal correspondence existing between the two phenomena studied possibly being associated with changes in the age distribution of animals during the evolutionary cycle of the small rodent population

IV 10 Consistency of the main results of this study

The results presented in section III 7 of this study showing a close correspondence between the incidence of endemic benign nephropathy in AC county and the prevalence of small rodents in northern Sweden are consistent with the documentation presented in section III 1 of a higher prevalence of the disease among people living more distantly apart i e in areas that constitute biotopes favourable for small rodents than among those living more closely grouped i e in built-up areas or in towns

VI REFERENCES

1 Adams L (ed): Population Ecology Dickenson Publ Comp Inc Belmont California 1970 LCCCN 75 - 118372

2 Andersson M & Hansson L Population regulation in small rodents - some hypotheses Fauna och Flora 69 113 1974

3 Chitty D Population processes in the vole and their relevance to general theory Can J Zool 38: 99 1960

4 Chitty D Animal numbers and behaviour In J R Dymont (ed) Fish and Wildlife: A memorial to W J K Harkness page 41 Longmanns Canada 1964

5 Christian D D & Davis D E : Endocrines behaviour and populations Science 146 1550 1964

6 Cöster C & Lublin H So-called Nephropathia Epidemica Act Med Scand suppl 246: 46 1950

7 Dolk H Nephropathia epidemica i Mellansverige (Värmland) Nord Med 71: 443 1964

8 Dorland s illustrated medical dictionary W B Saunders Company LCCCN 0 - 6383

9 Ellström J & Lindberger K Epidemisk nefrit - kontakt med gnagare Läkt 71 4482 1974

10 Englund J Vad reglerar en rävstams storlek Fauna och Flora 6 253 1970

11 Etholm B Nephropathia epidemica Tidskr n Laegef 80 386 1960

12 Fjellström K E Nephropathia Epidemica in Uppland Act Med Scand 167 111 1960

13 Freund J E Modern Elementary Statistics Prentice Hall Inc Englewood Cliffs N J 3rd ed 1967 LCCCN 66 - 29560

14 Hadders G : Sorksituationen i skogsfröplantagerna Institutet för skog förbättring Information 1967/68 1968/69 1969/70 Uppsala och Stockholm

15 Hansen E Atypi k akut n fritis Kliniske iakttagelser i en raekke tilfaelde Ugeskr Laeg 120: 908 1958

16 Hansson L Spring populations of small mammals in central Swedish Lapland in 1964 - 1968 Oikos 20: 431 1969

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I am also indebted to E Arvidsson and B Ek for statistical advice and to the staff of the County Administration s Unit of Regional Economics for generously supplying me with maps and information on the distribution and composition of the population in the county of Västerbotten

It has been a great privilege to have my English nursed by the gentle hand of J Robbins and the administrative proceedings competently supervised by my wife and K Holmqvist

It is gratefully acknowledged that this work was supported by grants from the Medical Faculty and Medical Clinic of Umeå University from the municipal authorities of Umeå and Vilhelmina from the County Council of Västerbotten from the Swedish Society of Medical Research (Ernst och Martha Janssons fond) and from Stiftelsen Clas Groschinskys Minnesfond

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1 Adams L (ed): Population Ecology Dickenson Publ Comp Inc Belmont California 1970 LCCCN 75 - 118372

2 Andersson M & Hansson L : Population regulation in small rodents - some hypotheses Fauna och Flora 69: 113 1974

3 Chitty D Population processes in the vole and their relevance to general theory Can J Zool 38: 99 1960

4 Chitty D : Animal numbers and behaviour In J R Dymont (ed) Fish and Wildlife A memorial to W J K Harkness page 41 Longmanns Canada 1964

5 Christian D D & Davi D E Endocrines behaviour and populations Science 146: 1550 1964

6 Cöster C & Lublin H : So-called Nephropathia Epidemica Act Med Scand suppl 246: 46 1950

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13 Freund J E Modern Elementary Statistic Prentice-Hall Inc Englewood Cliffs N J 3rd ed 1967 LCCCN 66 - 29560

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Kurt Nyström

31 Mouland G : Nephropathia epidemica 12 kasus fra Grane og Hattfjelldal i Nordland Fylke august 1973 - januar 1974 Tidskr n Laegef 95: 426 1975

32 Muri J W Nephropathia epidemica Nord Med 43: 290 1950

33 Muri J W Nephropathia epidemica Report of a case J Oslo City Hosp 3 192 1953

34 Muri J W : Nephropathia epidemica Leading article Tidskr n Laegef 95 456 1975

35 Myers J H & Krebs C J : Population cycles in rodents Sci Am 230 38 1974

36 Myhrman G En njursjukdom med egenartad symptombild Nord Med Tidskr 7 793 1934

37 Myhrman G : En ny infektionssjukdom i Nordsverige och Nordfinland Nord Med 28 2571 1945

38 Myhrman G : Nya fall av nephropathia epidemica Nord Med 40 1770 1948

39 Myhrman G Nephropathia Epidemica - a New Infectious Disease in Northern Scandinavia Act Med Scand 140 52 1951

40 Myhrman G Nya rön om nephropathia epidemica Sv Läkt 54: 3467 1957

41 Myrstener A : Ett ovanligt fall av nephropathia epidemica Sv Läkt 55 384 1958

42 National Central Bureau of Statistics:
Population and Housing Census 1960 1965 and 1970
Statistical Ab tra t of Sweden Stockholm 1960 - 1974

43 Nyström K Bergman B & Hoorn B Etiologiska studier vid nephropathia endemica benigna (nephropathia epidemica) Nord Med 65 782 1971

44 Oldberg S Om så kallade kryptogena akuta nefrite Nord Med 10: 1933 1941

45 Ornstein K & Söderhjelm L Nephropathia epidemica No d Med 69 618 1963

46 Ornst in K & Söderhjelm L Nephropathia epidemica Symptome und Verlauf Acta Soc Med Uppsal 68 286 1963

17 Hansson L : Personal communication

18 Hansson L & Andersson M : Factors governing small rodent outbreaks - a review of the development and implications of some hypotheses Symposium on bio-control of small rodents Lammi Biological station Finland May 1974 Mimeographed report

19 Hoorn B Bergman S Nyström K & Söderhjelm L : Viral Haemorrhagic Fevers Lancet 1144 1971

20 Hortling H : En epidemi av fältfeber (?) i finska Lappland Nord Med 30 1001 1946

21 Hälliqvist B Sporadiskt fall av nephropathia epidemica? Sv Läkt 46: 985 1949

22 Hörnfeldt B : Small rodent project in Umeå /Basinventering av gnagare (BIG) Department of ecological zoology Umeå University Mimeographed reports 1975 - 76

23 Knutrud O : Nephropathia epidemica Tidskr n Laegef 69 259 1949

24 Kuhlbäck B Fortelius P & Tallgren L G Renal Histopathology in a Case of Nephropathia Epidemica Myhrman A Study of Successive Biopsies Act Pathol et Microbiol Scand 60: 323 1964

25 Lancet: Viral haemorrhagic fevers Leading article 858 1971

26 Larsson T -B : Small rodent damage in Swedish forestry during the period 1900 - 1970 Institute of Forest Zoology Royal College of Forestry Research Notes Nr 14 Stockholm 1973

27 Larsson T -B : Damage caused by small rodents in Sweden Symposium on bio-control of small rodents Lammi Biological Station Finland May 1974 Mimeographed report

28 Lublin H : Till frågan om nephropathia epidemica Sv Läkt 46: 1166 1949

29 Lähdevirta J : Nephropathia epidemica in Finland A clinical histological and epidemiological study Ann Clin Res suppl 8 1971

30 Länsstyrelsen i Västerbottens län: Befolkningsutveckling i tätorter och glesbygd 1960 - 1970 Meddelande 1973 5 Umeå 1973

60 Trencsóni T & Keleti B : Clinical Aspects and Epidemiology of Haemorrhagic Fever with Renal Syndrome Analysis of the clinical and epidemiological experience in Hungary Akadámiai Kiadó Budapest 1971

61 Tungland B Nephropathia epidemica Nord Med 51 635 1954

62 Valnes K : Nephropathia epidemica Tidskr n Laegef 95 429 1975

63 Wold E Nephropathia epidemica 65: 2036 1968

64 Zetterholm S G Akuta nefriter simulerande akuta bukfall Sv Läkt 31 425 1934

47 Ornstein K & Söderhjelm L Nephropathia epidemica Med Welt 17: 898 1965

48 Radošević Z & Mohaček J : The Problem of Nephropathia Epidemica Myhrman - Zetterholm in Relation to Acute Interstitial Nephritis Act Med Scand 149: 221 1954

49 Siivonen L Structure of short-cyclic fluctuations in numbers of mammals and birds in the northern parts of the northern hemisfere Finnish Foundation for Game-Preservation Papers on Game Research No 1 1948

50 Skjörten F & Enger E : Nephropathia epidemica Den diagnostiske nytte av nyrebiopsi ved sporadisk opptreden Tidskr n Laegef 95: 423 1973

51 Siegel S Nonparametric Statistics for the Behavioral Sciences McGraw-Hill Book Company Inc 1956 LCCCN 56 - 8185

52 Snedecor G W & Cochran W G : Statistical Methods The Iowa State University Press Amos Iowa USA 6th ed 1967 4th print 1971 ISBNO - 8138 - 1560-6; LCCCN 67 - 21577

53 Ström J Akuta infektionssjukdomar 5 uppl Gleerup Lund

54 Stuhlfaut K Bericht über ein neues Schlammfieberähnliches Krankheitsbild bei Deutschen Truppen in Lappland Deutsch Med Wschr 69: 439 474 605 1943

55 Söderhjelm L : Hydatide Disease Epidemic Nephritis and Tularaemia in Northern Sweden Arch Environm Health 18: 127 1969

56 Söderhjelm L : Haemorrhagic Fever in Sweden J Infect Dis 124: 107 1971

57 Tast J & Kalela O : Comparisons between rodent cycles and plant production in Finnish Lapland Ann Acad Sci Fenn A IV Biol 186 1971 13 s

58 Toft R : Personal communication

59 Tomasson B Landlaeknir; Director general of Public Health Reykjavik Iceland: Personal communication

Consecutive number of case	Initials	Occupation or civil state	Sex	Age	Place of residence: category	Place of residence: municipal site	Date of onset of illness	Maximum registered value of body temperature; °C	Maximum registered value of proteinuria	Maximum registered value of azotaemia	Type of diuretic abnormality	Comments
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
1	FK G	Tractor driver	M	29	BU	1	59 12 01		4	NPM 112	P	Shivers
2	WKAR	Builder s mate	M	40	SP	9	60 01 21	40	10	11 6	O/P	
3	SGL	National forest ranger	M	33	BU	9	10 28	38 2	0 5	2 0	NO	
4	EP-OL	Engineer	M	24	SP	5	11 26	> 40	5	5 9	P	
5	WSH	Workshop manager	M	21	BU	9	11 27	40 2	4 0	3 0	NI	
6	AKA	Tractor driver	M	26	BU	9	12 10	39 5	2 5	1 5	NI	
7	BEP	Road-grader driver	M	40	SP	9	12 10	40 2	+	2 6	P?	
8	DTSJ	Forest worker	M	24	SP	5	12 25	39 5	3	1 1	P	Appendectomy performed
9	GK E	Farm owner	M	36	SP	9	12 26	NE?	6	8 5	P	
10	LED	Farm/forest worker	M	49	SP	9	12 31	NI	4	4 2	P	
11	OJA	Forest worker	M	16	SP	9	61 01 01	40	0 5	6 2	P	
12	LSM	Ore prospector	M	41	SP	5	01 23	39	5 5	4 8	P	
13	LTH	Farm worker	M	18	SP	9	02 25	38 2	+	NPM 65	NI	
14	LKO	Miner	M	30	SP	5	03 01	38 6	2 5	8 1	P	

Appendix Table A (pages 77-89) Demographic data for patients diagnosed as cases of endemic benign nephropathy in AC county northern Sweden December 1959 - April 1974 and some of the findings recorded during the acute phase of the disease

Notes

(a) The patients are tabulated in chronological order according to date of onset of illness. Beginning (May 1st) and end (April 30th) of seasons is indicated: - - - - - - - - - - -

(d) M: male; F: female

(e) Age in years on date of onset of illness

(f) The place of residence is classified as being situated either in a sparsely populated area (SP) or in a built-up area (BU) including that of a town (T)

(g) The municipal districts of AC county are designated as follows
Within the inland region: 1 - Sorsele 2 - Storuman 3 - Vilhelmina 4 - Åsele 5 - Norsjö 6 - Lycksele 7 - Vindeln
Within the coastal region: 8 - Vännäs 9 - Skellefteå 10 - Robertsfors 11 - Umeå 12 - Nordmaling

(j-l) Figures or symbols denote maximum value of parameter recorded or reported during the acute phase of the disease

(j) ^{o}C: Degrees Centigrade NE: Body temperature not elevated SE: slightly elevated

(k) Figures denote g protein per 1 000 ml of urine Using a strip test TR denotes trace amount of protein in urine + an amount of protein roughly corresponding to 30 mg per 100 ml of urine ++ to 100 +++ to 300 and ++++ to > 1 000 mg of protein per 100 ml of urine
Neg: Proteinuria not observed

(l) Figures denote creatinine concentration in mg per 100 ml of serum if not stated as NPN (non-protein nitrogen) or BUN (blood-urea nitrogen)

(m) Degree of diuretic abnormality is stated as volume of urine per 24 hours during stay in hospital the urinary volume recorded on day of admission being excluded O - oliguria (≤ 400 ml) P - polyuria (≥ 3 000 ml) NO - no diuretic abnormality recorded

NI No information available

? Information questionable

→ Denotes reference to information given in (n)

Con s cu- tive num- ber of cases	Ini tial	Occup tion or civil state	Sex	Age	Place of re idence: cate- gory	Place of re idence: mu- nici pal site	Date of onset of illnes	Maximum regis- tered value of: body tem- pera- ture; °C	Maximum regis- tered value of: pro- tein- uria	Maximum regis- tered value of: azot- aemia	Type of diure- tic abnor- mality	Comments
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
1	FK G	Tractor driver	M	29	BU	1	59 12 01		4	NPN 112	P	Shivers
2	WKAR	Builder s mate	M	40	SP	9	60 01 21	40	10	11 6	O/P	
3	SGL	National fore t ranger	M	33	BU	9	10 28	38 2	0 5	2 0	NO	
4	EP-OL	Engineer	M	24	SP	5	11 26	> 40	5	5 9	P	
5	WSH	Workshop manager	M	21	BU	9	11 27	40 2	4 0	3 0	NI	
6	AKA	Tractor driver	M	26	BU	9	12 10	39 5	2 5	1 5	NI	
7	BEP	Road-grader driver	M	40	SP	9	12 10	40 2	+	2 6	P?	Appendectomy performed
8	BTSJ	Forest worker	M	24	SP	5	12 25	39 5	3	1 1	P	
9	GK-R	Farm owner	M	36	SP	9	12 26	NE?	6	8 5	P	
10	LED	Farm/forest worker	M	49	SP	9	12 31	NI	4	4 2	P	
11	OJA	Forest worker	M	16	SP	9	61 01 01	40	0 5	6 2	P	
12	LSM	Ore prospector	M	41	SP	5	01 23	39	5 5	4 8	P	
13	LTH	Farm worker	M	18	SP	9	02 25	38 2	+	NPN 65	NI	
14	LKO	Miner	M	30	SP	5	03 01	38 6	2 5	8 1	P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
15	HAGA	Forest worker	M	14	SP	5	08 02	39 4	+	0 8	NO	
16	AG	Forest worker	M	36	SP	2	08 25	41	+++	NPN 258	P	
17	ÖUI	Domestic help	F	22	SP	9	62 04 13	39 4	T	0 9	NI	
18	RK-A	Forestry foreman	M	37	BU	5	08 13	39 5	3	2 6	O/P	
19	S-AO	Canteen manageress	F	46	BU	9	08 25	40 4	+	1 1	NI	
20	NECA	Farm owner s/forest worker s wife	F	42	SP	9	09 06	39 9	4 5	6 1	O/P	
21	AKGO	Forest worker	M	28	SP	5	11 01	38 4	2	1 4	P	
22	NHK	Housewife	F	56	BU	9	11 02	39	4	1 2	NI	
23	DHA	Forest worker	M	41	SP	5	11 04	38 8	2 5	2 1	NO	
24	EBK	Cook s assistant	F	36	SP	9	11 09	>38 6	+	3 8	P	
25	HAE	Manager	M	48	SP	6	11 15	39	3 5	6 6	O/P	
26	BTH	Excavator	M	34	SP	5	11 27	39 9	3 5	3 7	NO	
27	PTGV	Forest worker	M	28	SP	2	12 07	>37 4	7 5	2 4	P	
28	HLI	Seaside hotel manager	M	30	BU	9	12 30	40	2 5	1 4	P	
29	FJK	Taxi owner	M	37	BU	3	63 05 21	39	2 5	4 9	P	
30	HEK	Machinist	M	31	SP	6	05 30	39 5	6 2	6 6	P	
31	BRE	Farm owner	M	28	SP	1	07 01	> 40	12 5	10 2	P	
32	JAA	Housewife	F	38	SP	5	07 04	NI	+	1 8	P	
33	WIA	Lorry driver	M	31	SP	8	07 09	40 4	4 7	NPN 114	O	
34	KSB	Tractor driver	M	16	BU	6	08 02	39 5	4	2 4	P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
35	KHA	For st wo ker	M	6	SP	9	08 10	SE	10	1 1	NO	
36	DARA	Forest worker	M	39	SP	1	08 24	40 4	6 3	4 4	NO	
37	JFJ	Forest worker	M	69	SP	4	09 16	39 6	10	3 2	NO	
38	PSR	Farm owner/forest worker	M	62	SP	5	09 28	39	+++	3 2	NO	
39	BST	Laundress	F	50	SP	9	10 26	39	6 5	7 3	O	
40	EES	Forest worker	M	38	SP	4	11 06	→	3 3	1 6	P	Fever
41	BDT	Lorry driver	M	33	T	9	11 29	> 40	22	13 4	O/P	
42	BSA	Excavator	M	28	BU	7	12 01	40	+	3 8	NO	
43	MSV	Widow →	F	62	SP	1	12 03	→	1	NPM 145	NI	Lapp High fever
44	LK-O	Lorry driver	M	31	SP	9	12 21	39 8	5	7 2	O/P	
45	PHD	Telephone worker	M	53	T	9	64 03 11	39 6	4 5	5 9	NI	
46	LKM	Farm worker	M	59	SP	9	03 19	38	Neg	8 1	NI	
47	DEV	Farm owner s wife	F	60	SP	10	04 22	38 5	3	2 8	NO	
48	AGFR	Student	M	16	SP	9	05 11	37 8	1	3 3	NO	
49	ELV	Student	M	21	T	6	07 20	40 1	10	4 5	O/P	
50	PPE	Farm owner	M	53	SP	9	10 13	> 40	2	6 0	NI	
51	LEA	Farm owner s wife	F	40	SP	5	12 28	40 6	NI	8 9	O	
52	HM E	Sawmill worker	M	16	BU	11	65 07 02	38 2	7 0	1 9	NO	
53	LHV	Industrial worker	M	25	SP	9	11 16	39 5	5	3 9	O/P	
54	LOG	Factory worker	M	35	SP	9	11 28	40	3	2 9	P	
55	LGM	Cook s assistant	F	55	BU	12	12 01	40	++	5 9	O	
56	DGE	Timber measurer	M	31	BU	2	12 17	40 3	0 3	6 2	P?	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
15	HAGA	Forest worker	M	14	SP	5	08 02	39 4	+	0 8	NO	
16	AG	Forest worker	M	36	SP	2	08 25	41	+++	NPN 258	P	
17	ÖUI	Domestic help	F	22	SP	9	62 04 13	39 4	T	0 9	NI	
18	RK-A	Forestry foreman	M	37	BU	5	08 13	39 5	3	2 6	O/P	
19	S-AO	Canteen manageress	F	46	BU	9	08 25	40 4	+	1 1	NI	
20	NECA	Farm owner s/forest worker s wife	F	42	SP	9	09 06	39 9	4 5	6 1	O/P	
21	ÅKGO	Forest worker	M	28	SP	5	11 01	38 4	2	1 4	P	
22	NMK	Housewife	F	56	BU	9	11 02	39	4	1 2	NI	
23	DMA	Forest worker	M	41	SP	5	11 04	38 8	2 5	2 1	NO	
24	EBK	Cook s assistant	F	36	SP	9	11 09	>38 6	+	3 8	P	
25	HAE	Manager	M	48	SP	6	11 15	39	3 5	6 6	O/P	
26	BTN	Excavator	M	34	SP	5	11 27	39 9	3 5	3 7	NO	
27	PTGV	Forest worker	M	28	SP	2	12 07	>37 4	7 5	2 4	P	
28	HLI	Seaside hotel manager	M	30	BU	9	12 30	40	2 5	1 4	P	
29	PJK	Taxi owner	M	37	BU	3	63 05 21	39	2 5	4 9	P	
30	BEK	Machinist	M	31	SP	6	05 30	39 5	6 2	6 6	P	
31	BRE	Farm owner	M	28	SP	1	07 01	> 40	12 5	10 2	P	
32	JAA	Housewife	F	38	SP	5	07 04	NI	+	1 8	P	
33	WIA	Lorry driver	M	31	SP	8	07 09	40 4	4 7	NPN 114	O	
34	KSB	Tractor driver	M	16	BU	6	08 02	39 5	4	2 4	P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
78	NOK	Fore te	M	50	SP	8	10 27	39	+++	5 4	O/P	
79	LKE	Tr sport lorry driver	M	40	T	9	11 01	39 5	2	5 9	P	
80	LI	For st worker ⟶	M	47	SP	1	11 01	39 1	5 0	4 0	P	Brother of no 75
81	LSK	Carrier	M	52	SP	9	11 19	39	+++	1 5	MI	
82	AEM	Miner wife	F	46	BU	9	11 22	40	4	2 0	MO	
83	EH	Forest worker	M	60	SP	6	11 26	⟶	1	9 0	P	High grade fever
84	BMOI	Carpenter	M	35	BU	5	11 27	40	4 5	7 8	O/P	
85	LSA	Turner	M	31	BU	9	11 27	38 5	6	2 9	P	
86	BÖL	Cableway mechanic	M	22	SP	5	12 09	38 8	5	5 8	P	
87	LJE	Mechanic	M	36	BU	4	12 18	40	4	2 2	P	
88	EAM	Fore t/industrial worker	M	23	SP	5	12 19	⟶	+++	6 0	P	High grade fever
89	EGI	Student	F	16	T	11	67 03 07	NI	++	BUN 23	MI	
90	LEA	Confectioner	M	59	T	9	03 11	> 38	+	4 8	O	
91	SHI	Sawmill/factory worker	M	41	SP	9	04 09	37 6	13 5	8 0	O	
92	PPLK	Machinist/tractor driver	M	23	SP	1	05 27	39 6	9 0	6 6	P	
93	FF	District medical officer	M	44	BU	2	06 30	39 5	+++	10 8	O/P	
94	BKOA	Electrician	M	41	T	11	07 26	40	+	1 2	MO	
95	LBPJ	F rm owner	M	53	SP	9	07 30	38 8	25	9 0	O/P	
96	KLG	Political science student	M	24	T	11	08 17	40	5	1 8	O/P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
57	BLME	Housewife	F	49	SP	7	12 26	39	2	NPN 130	O/P	
58	EBEM	Nursing assistant	F	21	T	11	12 31	39 5	+++	2 1	NO	
59	HAG	Businessman	M	49	BU	5	66 01 18	40	+	1 1	O	
60	LBU	Miner	M	27	SP	5	04 03	40	7	4 0	P	
61	SHA	Farm owner	M	36	SP	9	06 01	39	+++	5 0	P	
62	ARÅ	Painter	M	29	BU	2	07 02	> 39	3 5	1 7	P	
63	BRJ	Tractor driver	M	27	SP	9	07 03	39 8	4 0	6 0	O/P	
64	OGSM	Bar assistant	F	34	SP	2	07 22	37 8	11	5 2	NI	
65	ASJA	Fitter	M	31	T	6	07 26	39	5	3 0	NI	
66	PEG	Foreman	M	33	BU	5	08 10	37 6	++	1 0	NO	
67	TH-G	Turner	M	18	BU	4	08 21	→	3 0	9 8	NO	Moderately elevated
68	EUE	Woodworker →	M	20	T	11	08 22	NE	2 8	2 7	P	Conscript
69	LBE	Policeman	M	39	T	11	09 06	39 8	+	2 0	P	
70	EH-E	Schoolboy	M	10	SP	1	09 16	39 5	3 2	5 1	NO	
71	JRA	Factory worker	M	33	SP	12	10 02	40 5	1 0	1 4	NO	
72	SEH	Motor mechanic	M	34	SP	7	10 06	39 6	+++	6 7	P	
73	LBK	Carpenter	M	19	BU	9	10 14	38 5	+++	1 8	NO	
74	MKG	Metalworker	M	31	SP	9	10 17	40	20	9 5	O/P	
75	LS	Garage attendant →	M	36	SP	1	10 21	38 2	12 5	10 0	O/P	Brother of no 80
76	NJE	Forest worker	M	28	BU	3	10 25	→	11 5	8 2	O/P	Fever
77	FÖN	Lorry driver →	M	22	T	11	10 26	40 5	+	2 8	O	Conscript

( )	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
78	NOK	Forestor	M	50	SP	8	10 27	39	+++	5 4	O/P	
79	LKE	Transport lorry driver	M	40	T	9	11 01	39 5	2	5 9	P	
80	LI	Forest work r →	M	47	SP	1	11 01	39 1	5 0	4 0	P	Brother of no 75
81	LSK	Carrier	M	52	SP	9	11 19	39	+++	1 5	MI	
82	ALH	Miner s wife	F	46	BU	9	11 22	40	4	2 0	NO	
83	EH	Forest worker	M	60	BP	6	11 26	→	1	9 0	P	High grade fever
84	BMOI	Carpent r	M	35	BU	5	11 27	40	4 5	7 8	O/P	
85	LSA	Turner	M	31	BU	9	11 27	38 5	6	2 9	P	
86	BÖL	Cableway mechanic	M	22	SP	5	12 09	38 8	5	5 8	P	
87	LJE	Mechanic	M	36	BU	4	12 18	40	4	2 2	P	
88	EAM	Forest/industrial worker	M	23	SP	5	12 19	→	+++	6 0	P	High grade fever
89	EGI	Stud nt	F	16	T	11	67 03 07	MI	++	BUN 23	MI	
90	LEA	Confectioner	M	59	T	9	03 11	> 38	+	4 8	O	
91	SHI	Sawmill/factory worker	M	41	SP	9	04 09	37 6	13 5	8 0	O	
92	PPLK	Machinist/tractor driver	M	23	SP	1	05 27	39 6	9 0	6 6	P	
93	FF	District medical officer	M	44	BU	2	06 30	39 5	+++	10 8	O/P	
94	BKOA	Electrician	M	41	T	11	07 26	40	+	1 2	NO	
95	LBPJ	Farm owner	M	53	SP	9	07 30	38 8	25	9 0	O/P	
96	KLG	Political science student	M	24	T	11	08 17	40	5	1 8	O/P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
97	SRE	Student	M	17	BU	4	12 28	40	17	1 5	NO	
98	SSA	Mining foreman	M	37	BU	9	68 10 18	> 39	4 5	5 7	O/P	
99	ÖKA	Drill worker	M	40	SP	5	11 13	40	++	2 9	O/P	
100	MEA	Shoemaker (retired)	M	53	BU	9	69 01 07	39	+	7 7	P	
101	JSH	Forest worker/farm owner	M	45	BU	9	01 14	40	3	3 2	P	
102	AKOA	Motor mechanic	M	19	BU	9	02 20	40 6	0 5	7 7	P	
103	ÖMY	Housewife	F	25	T	9	03 26	40 3	T	2 3	P	
104	HTG	Farm owner	M	27	SP	9	04 17	39 5	10	6 9	O/P	
105	LTE	Concrete worker	M	25	SP	5	07 10	39	0 5	6 5	NO	
106	ES	Nursing assistant	F	28	BU	5	08 27	40	12	12 6	O	
107	KASL	Hospital porter	M	30	T	9	09 24	40 1	16	3 4	O/P	
108	THBG	University student	M	23	T	11	10 06	39	++	11 0	O/P	
109	SLI	Machinist	M	30	SP	5	10 06	40 6	4 5	8 2	O/P	
110	KIL	Farm owner s wife	F	36	SP	5	10 17	40 6	5 5	9 0	O/P	
111	EAA	Reindeer keeper	M	27	SP	1	10 20	38	2 6	1 8	P	
112	PTE	Forest worker	M	42	SP	1	10 23	NE	15 0	5 4	P	
113	LSU	Lorry driver	M	19	BU	2	10 29	39	+++	13 0	O/P	
114	SHE	Tractor driver	M	32	T	9	10 30	⟶	20 0	6 6	P	Fever
115	TKR	Construction worker	M	28	SP	5	12 09	40	1 0	2 9	P	
116	JSA	Chauffeur	M	23	SP	9	12 12	NE	5	5 3	O/P	
117	ADA	Secondary school student	M	20	BU	9	12 20	> 40	4	4 8	P	
118	HSE	Dustman	M	43	T	11	12 21	⟶	+++	3 2	P	Fever

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
119	HMP-O	Fore t worker	M	35	BP	7	12 24	41	+++	5 3	NO	
120	LK E	Cl rk	M	40	BU	7	12 28	40	2 5	5 2	NO	
121	EJH	Special subject teacher	M	45	BU	9	70 01 02	40	+	1 7	P	
122	HOU-B	Housewife	F	26	BP	9	01 03	40	+	4 0	NI	
123	HTH	Truck driver	M	35	BU	12	01 14	39 5	+++	13 6	P	
124	HO-MK	Forest worker s wife	F	29	BP	9	03 15	39 6	+	2 0	P	
125	EUK	Forest worker s wife	F	55	BP	9	04 12	40	1	8 2	O/P	
126	HBK	Retired	F	72	BP	9	05 21	39 8	3	14 0	O/P	
127	JTG	Foreman	M	58	BP	3	06 11	40	+++	15 0	O/P	
128	LAR	Tractor driver/farm owner	M	41	BP	9	06 19	40	10	5 7	P	
129	ERG	Forest worker ⟶	M	23	BP	7	07 12	40	+	7 5	NO	Brother of no 131
130	NKS	Technical student	M	20	T	6	07 22	40 5	4 4	4 0	P	
131	ERA	Student ⟶	M	19	BP	7	07 27	40 4	3 1	1 1	NO	Brother of no 129
132	LH-O	Forest worker	M	30	BP	7	07 30	40	3 0	7 3	P	
133	FBEL	Garage attendant	M	25	BD	3	08 06	NE?	+	12 2	P	
134	JS	Supervisor s wife	F	42	T	9	08 07	40	+	4 9	O/P	
135	JG	Sawmill worker	M	28	BU	4	08 17	> 40	2 5	BUN 40	P	
136	WS	Hairdresser	M	34	T	11	08 17	41 1	+++	2 0	NO	
137	FTRD	Electrician	M	32	BP	8	08 18	39 5	Neg	BUN 17	NO	
138	JSB	Lineman	M	57	T	6	08 19	39 9	15 0	3 3	NO	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
97	SRE	Student	M	17	BU	4	12 28	40	17	1 5	NO	
98	SSA	Mining foreman	M	37	BU	9	68 10 18	> 39	4 5	5 7	O/P	
99	ÖKA	Drill worker	M	40	SP	5	11 13	40	++	2 9	O/P	
100	MEA	Shoemaker (retired)	M	53	BU	9	69 01 07	39	+	7 7	P	
101	JSH	Forest worker/farm owner	M	45	BU	9	01 14	40	3	3 2	P	
102	AKOA	Motor mechanic	M	19	BU	9	02 20	40 6	0 5	7 7	P	
103	ÖMY	Housewife	F	25	T	9	03 26	40 3	T	2 3	P	
104	HTG	Farm owner	M	27	SP	9	04 17	39 5	10	6 9	O/P	
105	LTE	Concrete worker	M	25	SP	5	07 10	39	0 5	6 5	NO	
106	ES	Nursing assistant	F	28	BU	5	08 27	40	12	12 6	O	
107	KASL	Hospital porter	M	30	T	9	09 24	40 1	16	3 4	O/P	
108	FHBG	University student	M	23	T	11	10 06	39	++	11 0	O/P	
109	SLI	Machinist	M	30	SP	5	10 06	40 6	4 5	8 2	O/P	
110	KIL	Farm owner s wife	F	36	SP	5	10 17	40 6	5 5	9 0	O/P	
111	EAA	Reindeer keeper	M	27	SP	1	10 20	38	2 6	1 8	P	
112	PTE	Forest worker	M	42	SP	1	10 23	NE	15 0	5 4	P	
113	LSU	Lorry driver	M	19	BU	2	10 29	39	+++	13 0	O/P	
114	SHE	Tractor driver	M	32	T	9	10 30	→	20 0	6 6	P	Fever
115	FKR	Construction worker	M	28	SP	5	12 09	40	1 0	2 9	P	
116	JSA	Chauffeur	M	23	SP	9	12 12	NE	5	5 3	O/P	
117	ABA	Secondary school student	M	20	BU	9	12 20	> 40	4	4 8	P	
118	HSE	Dustman	M	43	T	11	12 21	→	+++	3 2	P	Fever

( )	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
159	HBG	Cleaner →	M	19	T	11	12 01	38 6	++	3 8	NO	Conscript
160	WEB	Foreman	M	35	BU	11	73 01 14	39 4	+++	4 7	P	
161	BTA	Welder	M	41	SP	7	01 16	> 39	+++	1 9	NO	
162	JAHM	Confectioner	M	39	T	9	01 22	39	0 8	12 3	P	
163	FME	Housewife	F	33	T	6	01 23	> 40	1 5	12 0	P	
164	OAS	Farmer s wife	F	58	BU	7	01 31	38 5	0 9	7 3	P	
165	ABKS	Housewife	F	37	SP	4	02 05	39	+	6 5	P	
166	MSSA	Farmer s wife	F	50	SP	5	02 10	NI	+++	12 3	O/P	
167	BSAR	Farm owner s wife	F	30	SP	9	03 05	39	1 9	4 8	P	
168	HMA	Home help	F	19	SP	9	03 15	38 5	3	8 7	O/P	
169	FRJ	Cle k	M	25	T	11	03 20	39 5	++	3 5	P	
170	GHMA	Housewife	F	59	SP	1	03 26	40	3 3	5 2	O	
171	SR	Schoolboy	M	9	SP	9	04 11	39 8	6 5	2 2	NO	
172	LLM	Student	F	15	SP	9	04 22	40	0 7	9 4	O/P	
173	MAIE	Housewife	F	57	T	11	05 13	39	Neg	11 4	O/P	
174	JSG	Student →	M	16	SP	7	05 20	40 4	++	5 4	P	Son of no 176 and no 177
175	EB-GK	Colour sergeant	M	32	T	11	05 21	39	+++	5 1	P	
176	JEF	Wife (of no 177) →	F	40	SP	7	05 31	39 7	++	6 1	P	Mother of no 174
177	JB	Country division police commissioner s assistant/ farmer →	M	41	SP	7	06 06	39 8	+++	12 4	O/P	Father of no 174;dialysed
178	AFJ	Grinder	M	37	T	9	06 25	39 5	8	14 7	O/P	
179	PS-O	NI	M	26	T	11	06 27	39 9	+++	12 9	O/P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
139	LAA	Farm owner	M	33	SP	8	08 27	39 5	+	2 9	P	
140	HEA	Railway clerk	F	48	BU	9	08 30	39 5	5	6 2	P	
141	SEEL	Cook	F	40	T	9	09 02	39 5	7	3 2	O/P	
142	LKSS	Glassworker	M	30	SP	5	09 07	39 5	20	7 5	O/P	
143	OL-G	Student of philosophy	M	26	T	11	10 04	40 3	+	9 0	O/P	
144	MAB	Labourer	M	31	SP	3	10 11	> 39	15 0	7 3	O/P	
145	PKO	Labourer	M	22	BU	7	11 07	39 3	+++	6 9	O/P	
146	WJOG	Secondary school student	M	17	BU	7	11 22	41	3	3 2	NO	
147	BSE	Farm owner s wife	F	70	SP	5	11 25	41	+	3 4	O	
148	REE	Repairer	M	55	BU	11	71 02 28	39 9	+	7 2	P	
149	BKE	Student	F	19	SP	2	04 23	NI	T	9 9	NO	
150	BEJ	Teacher (retired)	F	65	T	11	09 08	38 3	++	5 9	P	
151	LSS	School canteen manageress (retired)	F	62	SP	8	09 08	40	Neg?	11 3	P	
152	JFE	Building worker	M	60	T	11	10 15	40	++	BUN 23	NO	
153	NP-L	Welder	M	30	T	9	11 11	39 5	5	1 6	P	
154	VVJJ	Lorry driver	M	20	SP	9	12 23	38 8	15 5	2 2	NO	
155	ASSE	Caterpillar tractor driver	M	33	BU	2	12 26	39 9	+	9 6	O	
156	LEJ	School caretaker	F	50	T	11	72 08 14	37 7	+++	15 2	P	Dialysed
157	JAS	NI	M	18	BU	2	10 23	39 5	+++	5 2	P	
158	KEH	Shop assistant	F	50	SP	2	11 25	39 9	0 5	8 6	P	

( )	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
202	BJE	Farm owner	M	64	SP	4	10 19	39 6	4 3	9 0	O/P	
203	SOS	Service mechanic	M	23	BU	11	10 25	39 5	Neg	1 0	NI	Out-patient
204	JNR	Farm owner	M	58	SP	1	10 26	→	NI	3 5	P	Influenza
205	SM H	Sorting clerk	M	27	T	11	10 27	38 2	+++	1 6	P	
206	MMT	Timber measurer	M	33	SP	2	11 02	→	++	1 6	NI	Fever
207	EIU	Nursing assistant	F	21	BU	7	11 03	40	+++	4 8	NO	High grade fever
208	GG	Housewife	F	48	BU	9	11 03	→	+	3 0	P	
209	DJB	Tractor driver	M	22	SP	2	11 04	38 5	++	1 9	NO	
210	KMR	Housewife	F	48	SP	11	11 06	39 5	+	4 8	O/P	Crippled by cardiac valvular disease
211	GGS	Plumber	M	51	T	11	11 10	40 4	+	2 3	P	
212	WST	Carpenter	M	32	SP	2	11 11	41	++	1 1	O	
213	ALS	Farmer	M	23	SP	2	11 11	40 6	++++	2 3	P	
214	ÖOM	Welder	M	42	BU	9	11 12	→	21	12 1	P	Fever
215	LI	Housewife	F	37	BU	2	11 14	39	+	3 4	P	
216	LUOA	Factory worker	M	26	BU	9	11 15	→	2 1	2 3	P	Fever
217	ÖSA	Housewife	F	40	SP	3	11 15	SE	+	8 3	NI	
218	LB	Painter	M	22	T	9	11 16	40	6 2	4 8	P	
219	GEG	NI	M	22	BU	3	11 17	→	3 5	1 6	NI	Fever
220	DKL	Lineman	M	34	BU	2	11 17	39	++	3 7	P	High grade fever
221	NP	Forest worker	M	66	SP	6	11 20	→	NI	5 6	O	
222	LLG	Stockroom worker	M	35	BU	9	11 26	→	9 5	8 5	O/P	Fever
223	SRI	Railway man	M	23	BU	9	12 01	40	+	2 9	NO	
224	RBS	Forest worker	M	53	SP	6	12 02	38 2	3 0	2 7	NI	
225	ABG	Shopkeeper	M	41	BU	10	12 02	40	+++	5 8	O/P	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
180	BLÅR	Self-employed	M	22	BU	5	07 03	40 2	+	3 5	P	
181	KCA	Graduate in medicine	M	27	T	9	07 10	40	+	4 5	P	
182	LSS	Engineer	M	28	T	11	07 21	39	+	5 6	P	
183	WKG	Nursing assistant	F	24	T	11	07 27	39	TR	3 7	NO	
184	BHH	Miner	M	29	BU	9	08 03	40	+	1 9	P	
185	HA	Journalist	M	50	BU	7	08 17	41	++	5 3	P	
186	VRV-A	Domestic help	F	23	BU	4	08 30	40 6	17 5	9 4	O/P	
187	NY	Stockroom worker →	M	21	BU	8	08 31	> 38	+	5 1	P	Conscript
188	NBM	Housewife	F	37	T	9	09 03	39	+	6 9	P	
189	LHI	Telecommunication technician	M	41	T	11	09 11	> 40	+++	11 4	P	
190	LLH	Farmer	M	34	BU	9	09 12	→	+	3 3	P	High grade fever
191	JLMÖ	Carpenter	M	28	BU	5	09 12	40 9	+	10 7	P	
192	HB	Housewife	F	41	BU	6	09 13	39 6	+++	16 0	O/P	
193	JT	Student	M	24	SP	11	09 15	→	1 4	8 4	O/P	Fever
194	HKM	Student	F	19	T	6	09 20	40	+++	2 5	NI	
195	HGA	Forest worker	M	47	SP	6	09 28	39	++	2 9	P	Out-patient
196	ELT	Baker	M	37	BU	4	10 01	40	0 5	4 4	O/P	
197	FP	Tractor driver	M	42	SP	1	10 09	40	NI	4 6	NI	
198	FJR	Farm owner	M	49	SP	9	10 12	→	15	4 1	NO	High grade fever
199	STB	Foreman	M	36	BU	9	10 12	→	4 5	8 4	P	High grade fever
200	HHL	Engineer	M	35	BU	11	10 15	39	TR	1 2	NO	
201	RAG	Electrical engineer	M	58	BU	9	10 19	NI	+	6 1	NO	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
47	KLA	Joiner	M	22	SP	9	01 26	→	++	6 1	P	Fever
48	PBE	Uphol torer	M	44	SP	7	01 26	40 7	++	11 8	O/P	
49	BM	Petrol truck driver	M	28	T	11	01 31	40 3	+++	11 6	P	
50	LBS	Metal worker	M	25	T	9	01 31	39 5	5 6	7 5	NI	
51	MKFR	Factory worker	M	18	SP	9	02 02	→	NI	4 4	NI	Fever
52	MRA	Taxidermist	M	35	SP	9	02 02	39 8	+	4 2	P	
53	LIV	Widow	F	86	BU	9	02 10	39	NI	2 7	NI	
54	AAV	Log-flo ter	M	65	SP	9	02 13	NI	+	8 5	NI	
55	ALM	NI	P	29	SP	1	02 15	→	NI	8 8	O/P	*High grade fever
56	SERS	Housewife	F	44	SP	9	02 15	40	6 4	6 3	O	Pensioner (epilepsy)
57	HMOR	Tractor driver	M	30	SP	9	02 19	→	5 7	2 2	NI	Fever
58	FU	Forest/farm worker	M	20	SP	1	03 06	39 5	4 0	15 2	O/P	
9	GEH	Schoolboy	M	10	BU	9	03 10	40	1 0	2 9	NO	
0	LHS	Foreman	M	49	BU	9	03 10	→	2 5	5 0	NI	Fever
1	LDA	Manager	M	42	T	9	03 11	→	1	9 0	P	Influenza
2	GEJ	Farm owner	M	55	SP	11	03 13	NE	++	6 5	NI	
3	HBJ	Blast furnace worker	M	64	T	9	03 16	→	+	2 5	P	Fever
	VEVI	Factory worker	M	31	BU	9	03 17	→	4 6	3 8	P	Fever
	HGA	Housewifo	F	58	SP	5	04 06	40	+	5 6	NO	
	LKR	Student	M	27	T	9	04 11	→	7 5	3 7	O/P	Pevor
	HGI	Housewife	F	52	SP	9	04 26	39	23 5	9 2	NI	

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(j)	(k)	(l)	(m)	(n)
226	HA	Motor winder	M	35	BU	9	12 03	→	5 0	6 0	P	Fever
227	VEJO	Plastic worker	M	39	SP	9	12 04	→	22 5	9 6	NI	High grade fever Father of no 231
228	LPMT	Schoolboy	M	8	SP	9	12 05	40 2	10	3 6	O	
229	WSG	Disabled pensioner →	M	39	BU	5	12 07	→	+	6 6	P	Mb Bechterew Shivers
230	HTG	NI	M	28	BU	3	12 12	→	+	3 1	NI	Fever"
231	VBU	Student	F	15	SP	9	12 12	39	+	3 8	P	Daughter of no 227
232	PK-I	Student	M	17	SP	2	12 12	NE	+++	3 0	NI	
233	HSI	NI	F	49	BU	6	12 15	→	+++	8 2	P	High grade fever
234	HKGH	Welder	M	21	BU	9	12 17	39 7	12 0	6 7	O	
235	HR	Farm owner	M	48	SP	6	12 21	38	NI	2 0	NI	
236	HSI	Farmer	M	25	SP	10	12 31	39 5	+++	9 7	P	
237	LKGS	Metal worker	M	25	SP	9	74 01 13	→	+	5 9	P	"Fever
238	FB-M	Shop assistant	F	30	SP	11	01 13	40	3 6	7 0	P	
239	FAK	Wood-carver →	M	50	SP	9	01 16	→	12	7 4	NI	Fever" Chronic myeloid leukemia (on prednisolone therapy)
240	LR	Boy	M	5	SP	9	01 18	SE	0 1	4 1	O	
241	BL-E	Office employee	M	29	SP	11	01 22	→	+++	3 6	NO	High grade fever
242	VGM	Accountant	M	29	BU	9	01 22	38 8	1 2	3 2	P	
243	ÖBN-O	Student	M	18	SP	9	01 22	NI	0 5	1 5	NO	
244	SRL	Welder	M	35	SP	9	01 23	→	30	13 8	P	High grade fever
245	JRM	Chauffeur	M	30	BU	9	01 24	40	++	8 6	P	
246	LT	Technical student	M	26	SP	9	01 25	40	+++	1 6	NI	

Age-group		MALES Ar SP	MALES Ar BU	MALES Ar AC	FEMALES Are SP	FEMALES Are BU	FEMALES Are AC	Bo h exes A es SP	Bo h exes A es BU	Bo h exes A es AC
	n P	520	9550	14757	4763	9738	14501	9970	19288	29258
	p P	10 0	14 0	12 3	10 7	13 8	12 6	10 3	13 9	12 4
	n C	28	32	60	7	3	10	35	35	70
	p C	27 2	30 7	29 0	20 6	11 5	16 7	25 5	26 9	26 2
39	C/P	(0 373)+	(0 233)+	(0 282)+	(0 102)+	(0 021)	(0 048)+	(0 244)+	(0 126)+	(0 166)+
	n P	6914	9226	16140	6160	9173	15333	13074	18399	31473
	p P	13 1	13 5	13 4	13 8	13 0	13 3	13 5	13 3	13 4
	n C	18	13	31	7	8	15	25	21	46
	p C	17 5	12 5	15 1	20 6	30 8	25 0	18 3	16 2	17 2
- 49	C/P	(0 181)	(0 098)	(0 133)+	(0 080)+	(0 061)+	(0 068)+	(0 133)+	(0 079)+	(0 101)+
	n P	10911	10781	21692	9202	10944	20146	20113	21725	41838
	p P	21 0	15 8	18 0	20 6	15 5	17 5	20 7	15 7	17 8
	n C	13	11	24	10	5	15	23	16	39
	p C	12 6	10 6	11 6	29 4	19 2	25 0	16 8	12 3	14 6
64	C/P	(0 083)	(0 071)-	(0 077)-	(0 075)+	(0 032)+	(0 052)+	(0 079)-	(0 051)-	(0 065)-
	n P	7048	5972	13020	6105	7095	13200	13154	13066	26220
	p P	13 5	8 8	10 8	13 7	10 1	11 5	13 6	9 4	11 2
	n C	3	0	3	2	2	4	5	2	7
	p C	2 9	0	1 4	5 8	7 7	6 6	3 6	1 5	2 6
65	C/P	(0 030)-	(0)	(0 016)-	(0 023)	(0 020)-	(0 021)-	(0 026)-	(0 011)-	(0 019)-
	n P	52185	68123	120308	44658	70458	115116	96844	138581	235425
ntire	p P	100 0	100 0	100 0	100 0	100 0	100 0	100 0	100 0	100 0
opu	n C	103	104	207	34	26	60	137	130	267
tion	p C	100 0	100 0	100 0	100 0	100 0	100 0	100 0	100 0	100 0
	C/P	(0 137)	(0 106)	(0 119)	(0 053)	(0 026)	(0 036)	(0 098)	(0 065)	(0 079)

Appendix Table B (pages 90-91)

Mean population of AC county for the census years of 1960 1965 and 1970 (n P) living outside (SP) or inside (BU) built-up areas of the county (AC) and number of cases of EBN (n C) diagnosed December 1959 - April 1974; distribution on sex and age-groups

Ratio of (C/P) proportion of cases (p C) to the corresponding proportion of population (p P); - the proportion of cases fell below or + above that of the population (Table IX page 30)

Within brackets is given the mean prevalence (number of cases per 1 000 inhabitants and year) of EBN for the period studied separately for each sub-group of the county population examined

Age-group		MALES			FEMALES			Both sexes		
		Area			Area			Area		
		SP	BU	AC	SP	BU	AC	SP	BU	AC
- 9	n P	6558	11239	17797	6091	10737	16828	12649	21976	34625
	p P	12 6	16 5	14 8	13 6	15 2	14 6	13 1	15 9	14 7
	n C	3	0	3	0	0	0	3	0	3
	p C	2 9	0	1 4	0	0	0	2 2	0	1 1
	C/P	(0 032) -	(0) -	(0 012) -	(0) -	(0) -	(0) -	(0 016) -	(0) -	(0 006) -
- 19	n P	9269	10800	20069	8133	10969	19102	17401	21770	39171
	p P	17 8	15 9	16 7	18 2	15 6	16 6	18 0	15 7	16 6
	n C	10	11	21	4	2	6	14	13	27
	p C	9 7	10 6	10 1	11 8	7 7	10 0	10 2	10 0	10 1
	C/P	(0 075) -	(0 071) -	(0 073) -	(0 034) -	(0 013) -	(0 022) -	(0 056) -	(0 041) -	(0 048) -
- 29	n P	6279	10555	16834	4204	11802	16006	10483	22357	32840
	p P	12 0	15 5	14 0	9 4	16 8	13 9	10 8	16 1	13 9
	n C	28	37	65	4	6	10	32	43	75
	p C	27 2	35 6	31 4	11 8	23 1	16 7	23 4	33 1	28 2
	C/P	(0 310) +	(0 243) +	(0 268) +	(0 066) +	(0 035) +	(0 043) +	(0 212) +	(0 134) +	(0 159) +

Appendix Table C Mean prevalence (number of cases per 1 000 inhabitants and year) of EBN diagnosed among the inhabitants of the 12 municipal districts of AC county northern Sweden, December 1959 - April 1974 The population figure is the mean of that for the census years of 1960 1965 and 1970 respectively; cf also Fig 9 page 42

	Municipal district	Sparsely populated area			Built-up areas			Entire district			Mean prevalence; ratio of district to the county mean	Land area; sq km	Mean number of inhabitants per sq km
		Mean population	Nos of cases	Mean prevalence	Mean population	Nos of cases	Mean prevalence	Mean population	Nos of cases	Mean prevalence			
1	Sorsele	3188	14	0 305	1822	1	0 038	5010	15	0 208	2 6	7494	0 67
2	Storuman	15432	10	0 128	4196	8	0 132	9628	18	0 130	1 6	7485	1 3
3	Vilhelmina	6074	3	0 034	3827	5	0 091	9901	8	0 056	0 7	8120	1 2
4	Åsele	7210	4	0 039	3844	6	0 108	11054	10	0 063	0 8	7118	1 6
5	Norsjö	7254	23	0 220	4397	8	0 126	11651	31	0 185	2 3	3384	3 4
6	Lycksele	6811	7	0 071	8741	9	0 072	15552	16	0 071	0 9	5636	2 8
7	Vindeln	5228	11	0 146	3432	7	0 142	8660	18	0 144	1 8	2727	3 2
Inland region		41197	72	0 121	30259	44	0 101	71456	116	0 113	1 4	41964	1 7
8	Vännäs	6893	5	0 050	5775	1	0 012	12668	6	0 033	0 4	1859	6 8
9	Skellefteå	26711	52	0 135	45650	52	0 079	72361	104	0 100	1 3	6846	10 6
10	Robertsfors	6045	2	0 023	2351	1	0 030	8396	3	0 025	0 3	1276	6 6
11	Umeå	11263	5	0 031	50383	30	0 041	61646	35	0 039	0 5	2212	27 9
12	Nordmaling	4892	1	0 014	3908	2	0 036	8800	3	0 024	0 3	1239	7 1
Coastal region		55804	65	0 081	108067	86	0 055	163871	151	0 064	0 8	13432	12 2
AC county		97001	137	0 098	138326	130	0 065	235327	267	0 079	1 0	55396	4 2

FROM THE DEPARTMENT OF MEDICINE, KAROLINSKA INSTITUTET
AT SERAFIMERLASARETTET STOCKHOLM SWEDEN

Cholesterol and Bile Acid Metabolism in Normo- and Hyperlipoproteinaemia

by Bo Angelin

Acta Medica Scandinavica

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I. ANGELIN B , EINARSSON K. HELLSTRÖM K and KALLNER, M Elimination of cholesterol in hyperlipoproteinaemia Clin Sci Mol Med 51 393 397 (1976)

II AHLBERG J , ANGELIN B , EINARSSON K. HELLSTRÖM K. and LEIJD B Biliary lipid composition and gallbladder disease in hyper lipoproteinemia Submitted for publication.

III ANGELIN, B EINARSSON K. HELLSTRÖM K. and LEIJD B Bile acid kinetics in relation to endogenous triglyceride formation in various types of hyperlipoproteinemia.

IV ANGELIN B EINARSSON K. HELLSTRÖM, K. and LEIJD B Effects of cholestyramine and chenodeoxycholic acid on the metabolism of endogenous triglyceride in hyperlipoproteinemia.

V ANGELIN B EINARSSON K. and HELLSTRÖM K. Evidence for the absorption of bile acids in the proximal small intestine of normo- and hyperlipidaemic subjects Gut 17 420 426 (1976)

VI. ANGELIN B BJÖRKHEM I. and EINARSSON K. Individual serum bile acid concentrations in normo and hyperlipoproteinemia as deter mined by mass fragmentography Relation to bile acid pool size Submitted for publication.

VII. AHLBERG J ANGELIN B BJÖRKHEM I. and EINARSSON K. Individual bile acids in portal venous and systemic blood serum of fasting man Submitted for publication.

VIII. ANGELIN B and BJÖRKHEM I. Postprandial serum bile acids in healthy man – evidence for differences in absorptive pattern between individual bile acids Gut in press (1977)

The papers will be referred to in the text by their Roman numerals as list ed above

CONTENTS

ABBREVIATIONS

C	Cholic acid
CD	Chenodeoxycholic acid
D	Deoxycholic acid
GBD	Gallbladder disease
HDL	High density lipoprotein(s)
HLP	Hyperlipoproteinaemia
LCAT	Lecithin cholesterol acyl transferase
LDL	Low density lipoprotein(s)
VLDL	Very low density lipoprotein(s)

Cholesterol is of vital importance as a structural component of all cellular and intracellular membranes and serves as a precursor for steroid hormones and bile acids. The recognition of cholesterol as an important factor in the pathogenesis of clinically important conditions such as atherosclerosis and cholelithiasis has promoted a vast interest in the formation, transport, and degradation of cholesterol in man. As a contribution to our knowledge in this field, the aim of the investigations summarized in the present thesis was to study some aspects of cholesterol and bile acid metabolism in normo- and hyperlipoproteinaemic man.

ABBREVIATIONS

C	Cholic acid
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VLDL	Very low density lipoprotein(s)

According to current concepts most if not all LDL is derived from VLDL breakdown via IDL (43, 60) LDL is the major vehicle for cholesterol in human plasma, and as evidenced from studies in cultured fibroblasts (23 24) the uptake and degradation of LDL is critically dependent on a membrane surface receptor specific for these lipoproteins In analogy with other metabolic receptors the LDL receptor' itself appears to be subject to homeostatic regulation (21). The major site of LDL catabolism is not known, but there is some indication that the extrahepatic tissues may play an important role (103)

HDL (high density lipoproteins α lipoproteins) within the density range 1.063 1.21 are the smallest lipoproteins (90-120 Å) Protein (about 50%) and phospholipids (about 35%) are the major constituents, whereas cholesterol and triglycerides account for about 15 and 5% respectively HDL are synthesized by the liver and the intestine (43 60) contain apoproteins necessary for the lipoprotein lipase reactions and provide esterified cholesterol to VLDL and LDL by means of the LCAT (lecithin. cholesterol acyl transferase) reaction. HDL may also play an important role in the transport of cholesterol from peripheral tissues to the liver (60)

TRIGLYCERIDE METABOLISM

Dietary fat is hydrolyzed in the lumen of the small intestine and subsequently absorbed mainly as monoglycerides and fatty acids Triglycerides are resynthesized in the mucosal cells and secreted into the lymph vessels as chylomicrons and VLDL. The proportion between the amounts of fat transported in chylomicrons and in VLDL seems to be influenced by the amount of fat that has been absorbed (50) VLDL continue to be secreted from the intestine long after the disappearance of chylomicrons from the circulation.

In the liver triglycerides may be formed from de novo synthesized fatty acids and from free fatty acids liberated by lipolysis in adipose tissue Under fasting conditions and during ordinary dietary conditions, plasma free fatty acids are virtually the sole precursors for hepatic VLDL triglycerides (55) After ingestion of carbohydrate-rich diets hepatic fatty acids appear to play a significant role in the formation of VLDL (79) The rate-limiting step(s) in triglyceride (and VLDL) synthesis are not known, and our insight

BACKGROUND

LIPOPROTEINS AND LIPOPROTEIN METABOLISM

Being insoluble in water lipids are transported in plasma bound to proteins Free fatty acids are mainly complexed to albumin while triglycerides free and esterified cholesterol, and phospholipids are present in lipoproteins In triglyceride-rich lipoproteins these complexes contain a core of the apo lar lipids – triglycerides and cholesteryl esters – and a surface of the more polar lipids – free cholesterol and phospholipids – together with apoproteins (60 77)

Chylomicrons are the largest lipoproteins, with a diameter of 300 5000 Å and a density of less than 0 95 (g/ml) The protein content is only 0 5 2% while 80-95 2-12 and 3-15% of the weight is made up of triglycerides phospholipids, and cholesterol respectively (49, 60 77) Chylomicrons carry exogenous fat from the intestine to other tissues where the triglyceride core is hydrolyzed by the enzyme lipoprotein lipase Due to rapid clearance from the circulation chylomicrons are not present in the plasma of healthy fasting man

VLDL (very low density lipoproteins pre-β-lipoproteins) have a diameter of 280-700 Å and contain triglycerides (50-70%) cholesterol (10 25%) phospholipids (15 25%) and protein (10-13%) giving a density of 0 95 1 006 (49 60 77) Most VLDL are synthesized in the liver but the intestine is also capable of VLDL formation (50) These lipoproteins transport endogenous triglycerides to other tissues especially adipose and muscular tissue where the removal mechanisms appear to be common for endogenous and exogenous triglycerides (25) During the breakdown of VLDL there is an exchange of apoproteins with other lipoproteins The remnant particles IDL (intermediate density lipoproteins) deliver much of their cholesterol to the liver (45 60) and are subsequently degraded into LDL (43 60)

LDL (low density lipoproteins β-lipoproteins) have a density of 1 006 1 063 and a diameter of 210 250 Å They are composed of 20 25% protein 40-45% cholesterol 20 25% phospholipids and only about 10% triglycerides (49 60)

of cholesterol is absorbed (18, 67 89) incorporated into chylomicrons (and VLDL) and finally delivered to the liver a key organ in cholesterol metabol ism The hepatic cholesterol is used in the formation of plasma lipoproteins (about 8 12 mmol/day) and bile acids (about 1 mmol/day) Furthermore, about 2 5 mmol of cholesterol is excreted with the bile each day (34 104)

Although most tissues in man are capable of synthesizing cholesterol, hepatic and intestinal cholesterogenesis clearly predominate (34 104) The rate limiting step in cholesterol biosynthesis has been located to the forma tion of mevalonate from HMG CoA (β hydroxy β methylglutaryl CoA) a reaction which is catalyzed by the microsomal enzyme HMG CoA reductase (for a review see 93) This enzyme is subject to a sensitive feed back control still incompletely known in its details As chylomicrons seem to be more effective than VLDL in suppressing cholesterol synthesis in the rat liver exogenous rather than endogenous cholesterol may be of major importance in this respect (111) Intestinal cholesterogenesis appears to be regulated primarily by bile acids excreted into the intestine (33) although intestinal cholesterol may have some effect too (96) Studies in the rat (53 97) and in man (4 30) indicate that bile acids also inhibit hepatic HMG CoA reductase by negative feed-back regulation. In several tissues cholestero genesis appears to be depressed due to feed back inhibition by LDL, mediat ed over the LDL-receptor mentioned above (10)

Only small amounts of cholesterol are excreted through the skin (15) and eliminated as steroid hormones in the urine (73) under steady state conditions The total formation of cholesterol should thus equal the combined faecal excretion of bile acids and neutral steroids minus dietary cholesterol intake

BILE ACID METABOLISM

Bile acids are formed in the liver from cholesterol. The first and rate-limit ing step the microsomal 7α-hydroxylation of cholesterol is subject to feed back inhibition by bile acids returning to the liver via the portal vein (for a review see 32) In man, the two primary bile acids formed are C (cholic acid) and CD (chenodeoxycholic acid) (Figure 2) Under normal conditions C represents about two thirds of the bile acids produced (37 109) Bile acids are secreted in the bile conjugated with glycine or taurine, stored in the gallbladder and subsequently released into the duodenum After participat

into the mechanisms regulating triglyceride formation and its incorporation into VLDL is incomplete

Fatty acids liberated by hydrolysis of chylomicron and VLDL triglycerides by the action of lipoprotein lipase, are taken up and incorporated into stor age triglycerides (92 110) The latter may be mobilized as free fatty acids in the lipolytic process, which is under intricate hormonal control (27) A triglyceride lipase of hepatic origin is present in post heparin plasma it has been suggested to be active in the degradation of IDL (60 65)

CHOLESTEROL METABOLISM

A highly simplified over-all schedule of cholesterol turnover in man is pre sented in Figure 1 Dietary cholesterol mixes in the intestinal lumen with cholesterol secreted in the bile and from mucosal cells (34) About 30 to 50%

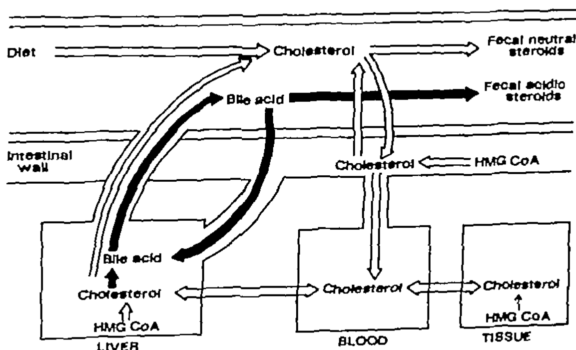


Figure 1 Cholesterol metabolism in man (see text)

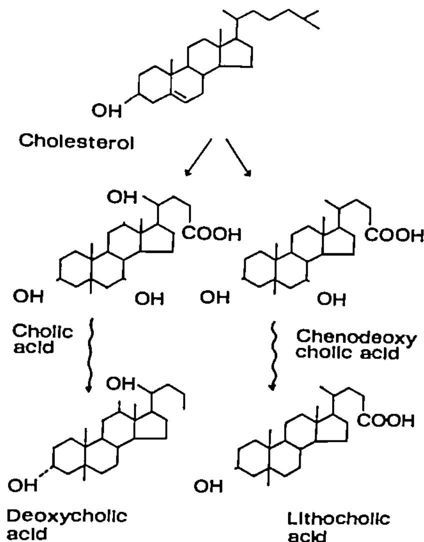
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igure 2 Formation of major bile acids in man (see text)

g in fat absorption in the upper small intestine bile acids are efficiently eabsorbed mainly by active transport in the distal ileum Intestinal bacte a deconjugate and dehydroxylate the primary bile acids whereby D (deoxy- olic acid) is formed from C and lithocholic acid from CD (Figure 2) The rmer is efficiently reabsorbed in the intestine while the latter is mainly st in the faeces Consequently the major bile acids present in human bile e C CD and D normally in the proportions 1 1 1·0 9 (37) The ratio tween C and CD pool sizes is often higher than the ratio between the con ntration of the two acids in duodenal bile a discrepancy suggesting that and CD differ in rate of enterohepatic circulation.

Via the portal vein, the bile acids reach the hepatic sinusoids, where they are cleared by the liver and reexcreted in the bile. Virtually nothing is known about the portal venous concentration of bile acids in healthy man or about the extraction process its efficiency and possible differences between the individual bile acids The concentration of bile acids in peripheral blood serum is very low (95) and little is known about its relation to the total bile acid content. The total bile acid pool undergoes continuous enterohepatic circulation, the daily excretion of bile acids in the bile amounting to about 50 mmol. Most of this material is reabsorbed and the amounts lost in the faeces of healthy subjects average 1 mmol/day (74)

HYPERLIPOPROTEINAEMIA

Serum lipoprotein levels may increase in patients with diseases such as diabetes mellitus hypothyroidism nephrosis biliary obstruction, and dysglobulinemia (47)

There are also primary forms of hyperlipoproteinaemia (HLP) i.e. disorders of familial or unknown origin. In 1967 Fredrickson et al (49) developed a system for the classification of primary HLP based on five phenotypes Slightly modified (12) this system is now widely accepted, and its principal outlines are shown in Table 1

Table 1 Classification of hyperlipoproteinaemias (12)

Type	Lipoprotein elevated
I	Chylomicrons
IIa	LDL (β lipoprotein)
IIb	LDL + VLDL (β and pre-β lipoprotein)
III	IDL (floating β -or "broad β" lipoprotein)
IV	VLDL (pre-β lipoprotein)
V	chylomicrons + VLDL (pre β lipoprotein)

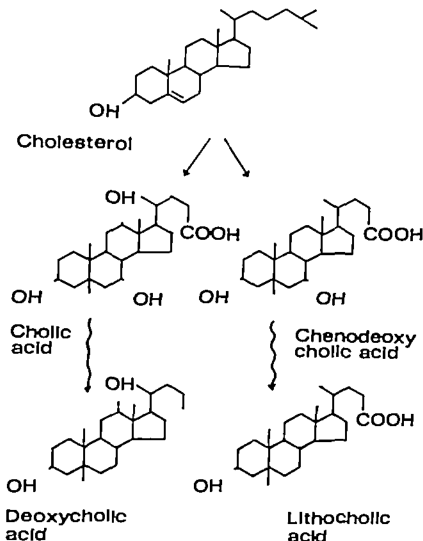


Figure 2. Formation of major bile acids in man (see text)

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An important discovery in recent years was the recognition that the identi fication of a phenotype does not necessarily define a genotype (51 78) Three different, apparently dominant genetic traits have been discribed. familial hypercholesterolaemia familial hypertriglyceridaemia and familial com bined hyperlipidaemia (51, 81) None of the traits was characterized by a specific lipoprotein pattern. The type II and IV lipoprotein phenotypes are the ones encountered most frequently (48 49), and the discussion below will be confined to these disorders

Type II HLP This lipoprotein pattern may be seen in familial hypercholes terolaemia familial combined hyperlipidaemia or polygenetic hypercholes terolaemia (78) In its classical form familial hypercholesterolaemia is characterized by tendon xanthomata, corneal arcus and a high incidence of cardiovascular disease According to in vitro studies the LDL elevation appears to be associated with defects in the LDL receptors In cultured skin fibroblasts from patients with heterozygous familial hyper cholesterolaemia,the content of LDL receptors is reduced by about 50% (20) Virtually no receptors may be found in the homozygous patient The lipoprotein pattern in familial hypercholesterolaemia is generally that of type IIa but occasional cases of type IIb are seen (22) In the other and more common forms of type II HLP no LDL receptor' deficiency has been described Type IIa lipoprotein pattern is generally not associated with obesity, carbohydrate intolerance, or hyperuricaemia (22 48) which may be seen in some traits of HLP type IIb

Type IV HLP The underlying metabolic defect(s) in type IV HLP have not been characterized and the clinical picture varies Obesity and impaired glucose tolerance are encountered in about 50% of the patients Hyperuri caemia is frequently observed and the incidences of GBD (41) and coronary heart disease are above normal (54)

Lipid and lipoprotein metabolism in HLP Studies of the metabolism of radio labelled LDL in patients with heterozygous familial hypercholesterolaemia have revealed a decreased fractional turnover rate of the LDL particles (68 99) The formation of LDL appears to be normal

The increased VLDL levels in type IV HLP may be due to overproduction of VLDL triglycerides (1 84 87 90) decreased clearance (16 35 56 88 94) or both (62 83) In agreement with the latter concept,kinetic studies with VLDL labelled in the apoprotein moiety (100) showed an increased for mation of VLDL in six of eight subjects and a decreased clearance of the

lipoprotein in four VLDL-metabolism in type IIa HLP appears to be within normal limits (100)

Cholesterol synthesis has been reported to be normal in type II HLP (17, 28 52, 80 106), while synthesis of bile acids was found to be subnormal normal (37 74) The most apparent abnormality however is a reduced formation of C (37) resulting in a subnormal C-CD synthesis ratio

Type IV HLP is frequently but not invariably associated with an increased elimination of cholesterol as bile acids (37) mainly due to an elevated production of C Similar findings with regard to faecal bile acid excretion have been reported (74) Apparently patients with type IV HLP are heterogeneous both with regard to triglyceride cholesterol and bile acid metabolism.

CHOLESTEROL GALLSTONE DISEASE

Cholesterol secreted in the bile is rendered soluble by forming micelles with lecithin and bile acids (2 91) Supersaturation of the bile with cholesterol may occur in response to factors influencing the secretion of bile acids phospholipids and cholesterol disproportionately According to current view supersaturation of the bile precedes and predisposes to formation of cholesterol gallstones in man (2 91) The exact limits of cholesterol solubility – conveniently expressed as indices (2 57 59 108) – are still under debate. An increased saturation of cholesterol in bile is often observed in obesity (6 14) and during treatment with contraceptive steroids (13, 66) and clofibrate (86) i.e conditions linked to an abnormally high incidence of gallstone disease (18, 29)

In a previous study (41) subjects with type IV HLP (in contrast to those with type IIa) appeared to carry an increased risk of gallstone formation. Patients with the type IIb pattern were not included in that study

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MATERIAL AND METHODS

The subjects. The patients (I VI) were those consecutively admitted because of HLP during the time of the study The normolipidaemic control subjects (I V VI, VIII) were healthy volunteers mainly members of the staff The study reported in paper VII comprised patients admitted to the Department of Surgery for operation of uncomplicated gallstone disease. An informed consent was obtained from all subjects Excluded were patients with HLP types III and V and those with evidence of intestinal hepatic or renal disease heart incompensation, hyper and hypothyroidism and those addicted to alcohol or narcotics In some studies (II IV) patients with overweight (> 120% of ideal weight) were rejected.

Classification of HLP WHO recommendations (12) were used for classification of HLP Serum and β lipoprotein cholesterol, serum triglycerides and the lipoprotein pattern as evidenced by agarose electrophoresis were determined. The upper normal limit was set at 7 2 mmol/l for serum cholesterol (7 0 mmol, l in I) at 5 4 mmol,'l for β lipoprotein cholesterol, and at 2 0 mmol l for serum triglycerides

Experimental procedure. The patients were hospitalized, and standardized dietary conditions were used (I IV VI) This diet was of natural type. The caloric intake was adjusted to keep the body weight constant. No antibiotics or other drugs known to affect lipid metabolism were given during the study or the preceding months A detailed description of the expermental procedure is given in each paper

Bile acid kinetics were determined after oral administration of [24 ^{1} C] labeled C and CD Duodenal bile was obtained through a thin polyvinyl tube in the fasting state at intervals of 1 3 days The bile acid pool size, half life, and synthesis were determined as outlined by Lindstedt (71) [^{3}H] CD was originally used as tracer substance (I) It was later on replaced by [C] CD to avoid the slight error caused by non-specific losses of tritium in the body (38)

AIMS OF THE PRESENT STUDY

1 To study cholesterol metabolism in various types of hyperlipoproteinaemia by measuring the net steroid 'balance and the biliary lipid composition. (I, II)

2 To study the interrelationship between bile acid and endogenous plasma triglyceride metabolism in patients with different types of HLP (III, IV)

3 To determine the serum concentrations of individual bile acids in control subjects and patients with HLP (VI)

4 To characterize the enterohepatic circulation of individual bile acids (V VII, VIII)

GENERAL RESULTS

CHOLESTEROL METABOLISM IN HLP (I, II)

Net steroid 'balance' Altogether 69 subjects were studied with regard to the faecal excretion of neutral steroids (cholesterol, coprostanol and coprostanone) and the formation of C and CD The intake of cholesterol was about 0.25 mmol/day In the control subjects the faecal excretion of cholesterol and its neutral metabolites averaged 1 07 ± 0 13 mmol/day Similar values were observed in HLP type IIa and type IIb whereas the patients with type IV lipoprotein pattern tended to have a higher excretion of neutral steroids (mean 1 48 ± 0 17 mmol/day)

In the control subjects as well as in the patients with type IIa and type IIb HLP the formation of bile acids (C + CD) averaged about 1 mmol/day Type IV HLP was associated in general with an increased bile acid synthesis 2 31 ± 0 22 mmol/day As seen in Figure 3 the total elimination of cholesterol was similar (about 2 mmol/day) in the controls and the patients with type IIa and IIb HLP Approximately equal amounts of cholesterol appeared to be eliminated as bile acids and neutral steroids As described previously (37) the formation of C represented about 65% of the total bile acid synthesis in the controls but only 47% in subjects with type IIa and type IIb HLP A clearly different pattern was seen in the patients with HLP type IV Mainly due to the increased formation of bile acids (Figure 3) the cholesterol elimination was almost twice as high as that encountered in the control subjects C accounted for 70% of total bile acids produced (cf 37)

Neglecting urinary and skin excretion of steroids the *net 'balance* was calculated as bile acid synthesis + faecal neutral steroid excretion – dietary intake. The balance averaged 1 83 ± 0 22 mmol/day in the controls 1 60 ± 0 15 and 1 61 ± 0 19 mmol/day in HLP type IIa and type IIb, respectively The net 'balance in HLP type IV was significantly higher 3 53 ± 0 23 mmol/day than that of the controls ($p < 0.001$) However the former group was heterogeneous and in about 50% of the patients the net steroid balance was within the normal range. Net steroid 'balance did not correlate with

Neutral faecal steroids Pooled faecal samples collected during 7 to 10 days were used, in order to minimize the effects of irregular faecal flow The neutral steroids (cholesterol coprostanol and coprostanone) were determin ed by gas-liquid chromatography after extraction and isolation by thin layer chromatography (44)

Endogenous plasma triglyceride kinetics were determined as described by *Farquhar et al (46) and later on by Nikkilä and Kekki (63 82 83)* [2-^{3}H] glycerol was injected intravenously after an overnight fast. Venous blood samples were collected repeatedly and analyzed for plasma radioactivity and triglyceride concentration. Analysis of the radioactivity decay curve was performed with a digital computer Only single exponential curves were accepted Altogether about 10% of curves were rejected for this reason or because of unstable triglyceride concentrations

Serum bile acids An assay based on combined *gas chromatography – mass* spectrometry was developed (VI)

Details of the analytical procedures employed are given in the individual papers

Statistical procedure Data are presented as mean ± SEM The χ^2 test Student s t test and paired t test and the Wilcoxon rank sum test have been used (102) Linear regressions have been calculated with the method of least squares and their significances tested by estimating the correlation coeffi cient r (102)

molar percentage of cholesterol, bile acids and phospholipids in duodenal bile was 7.2 ± 0.2 71 2 ± 0 7 and 21 6 ± 0 6% respectively As compared to HLP type IIa, HLP type IIb and type IV were associated with an increased molar percentage of cholesterol 10.2 ± 0 6% and 9 9 ± 0 6% respectively The lithogenic indices according to Admirand and Small (2) and Hegardt and Dam (57) and Holzbach (59) were also significantly higher in both type IIb and type IV than in type IIa HLP ($P < 0\ 001$)

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composition and the occurrence

The occurrence of GBD was de
patients consecutively admitted
frequency of GBD was 8, 18 and
females with type IIa, IIb and
Altogether 138 patients were 40-

The formation of plasma triglycerides ave ... µmol kg h
in type IIa HLP The corresponding values obtained in type IIb (20 7 ± 1 9 µmol kg h ¹) and type IV HLP (22.1 ± 1 4 µmol kg ¹ h) were significantly higher In general, males tended to produce more triglycerides

sex, glucose intolerance, body weight serum cholesterol or triglyceride concentration.

Biliary lipid composition and the occurrence of GBD in HLP (II)
The occurrence of GBD was determined in 210 hyperlipoproteinaemic patients quency of GBD was 8 18 and 42% in males and 22 48 and 72% in females patients were 40 59 years old. The incidence of GBD in this group was compared with the findings in three age-matched necropsy series from Malmö General hospital (72 107 112) and was signicantly higher in the male ($P < 0\ 001$) and the female ($P < 0\ 025$) patients with type IV HLP A tendency to an increased frequency of GBD although not statistically significant was also seen in females with type IIb HLP

Altogether 38 non-obese hyperlipoproteinaemic patients without GBD were studied with regard to bile lipid composition. In type IIa HLP the mean

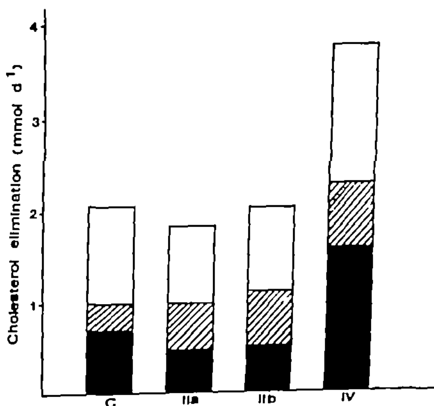


Figure 3 Elimination of cholesterol (mmol d^{-1}) in control subjects (C) and in patients with hyperlipoproteinaemia
■ cholic acid ▨ chenodeoxycholic acid □ faecal neutral steroids

molar percentage of cholesterol bile acids and phospholipids in duodenal bile was 7 2 ± 0 2 71 2 ± 0 7 and 21 6 ± 0 6% respectively As compared to HLP type IIa, HLP type IIb and type IV were associated with an increased molar percentage of cholesterol 10 2 ± 0 8% and 9 9 ± 0 6% respectively The lithogenic indices according to Admirand and Small (2) and Hegardt and Dam (57) and Holzbach (59) were also significantly higher in both type IIb and type IV than in type IIa HLP (P < 0 001)

lusions Patients with type IIa or IIb HLP eliminated normal amounts olesterol as bile acids and faecal neutral steroids More than half of atients with type IV HLP displayed a net steroid 'balance above the ul limit. The average ratio between the amount of C and CD synthe- l was subnormal in HLP type IIa and type IIb but supranormal in HLP IV

P type IV is to a high extent associated with an increased saturation of sterol in the bile. This finding may have some bearing to the increased rrence of GBD in patients with this disorder

E ACID AND PLASMA TRIGLYCERIDE KINETICS IN HLP TYPE ND IV (III, IV)

al conditions (III). Bile acid and plasma triglyceride kinetics were deter ed in 4 patients. In agreement with previous studies (37 cf I) the for ion of bile acids was lower in type IIa (0 72 ± 0 07 mmol/day) and type 0.83 ± 0 12 mmol/day) than in type IV HLP (1 43 ± 0 16 mmol/day) s difference was mainly due to an enhanced production of C which ave- ed 0.95 ± 0 11 mmol/day in type IV and 0 42 ± 0 04 mmol/day in type IIa. vident from figure 4 the differences between the types of HLP concer t bile acid production were still present when expressed as μmol kg⁻¹

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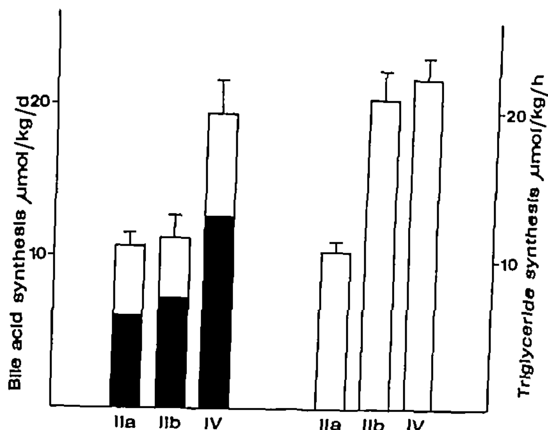


Figure 4 Synthesis of bile acids (□ cholic acid, ■ chenodeoxycholic acid µmol/kg/d) and triglycerides (µmol/kg/h) in patients with hyper lipoproteinaemia type IIa, IIb and IV

than females The mean fractional turnover rate of triglycerides was 0 188 ± 0 008 h^{-1} in type IIa and 0 177 ± 0 11 h^{-1} in type IIb Significantly lower values 0 147 ± 0 011 h^{-1} were encountered in HLP type IV

A positive correlation was obtained between the formation of plasma triglycerides and that of C in HLP type IIa (r = +0 69 P < 0 001) and type IV (r = +0 70 P < 0 001) A similar relationship was seen for (C + CD) with r = +0 59 (P < 0 01) in type IIa and r = +0 69 (P < 0 001) in type IV HLP The production of CD and triglyceride correlated in HLP type IV (r = +0 67 P < 0 01) No such relationship was found in the patients with the type IIa pattern

Treatment with cholestyramine and CD (IV) The triglyceride formation was reinvestigated in 26 hyperlipidaemic subjects For 2–4 months before the second study 14 of the patients had been treated with cholestyramine (12 g/day) The other 12 patients had been administered CD (1 9 mmol = 750 mg/day)

Previous data have demonstrated that cholestyramine treatment results in a stimulation (40) and CD therapy in a depression (61) of the bile acid production. During administration of cholestyramine, the formation of plasma triglycerides increased in all patients with HLP type IIa, the means before and during therapy being 9 7 ± 1 2 and 12.8 ± 1 5 µmol kg h respectively Cholestyramine treatment also stimulated the fractional turnover rate, which increased from 0 176 ± 0 014 to 0.230 ± 0 017 µmol kg ¹ h In the five patients with type IV HLP studied, cholestyramine therapy had no consistent effects on plasma triglyceride kinetics

During feeding with CD, the synthetic rate of plasma triglycerides decreased in subjects both with HLP type IIa (from 13 1 ± 1 2 to 7 9 ± 0 5 µmol kg h) and type IV (from 23 6 ± 3 7 to 15 5 ± 1 8 µmol kg h) In the whole series of patients the fractional turnover of plasma triglycerides decreased from 0 169 0 013 to 0 133 ± 0 013 h A 15% reduction of plasma triglyceride levels was seen

Conclusions. Under basal conditions in patients with HLP type IIa or IV the rate of degradation of cholesterol to bile acids appears to reflect the rate of plasma triglyceride formation. Upon stimulation of bile acid production by a bile acid sequestering agent the production of plasma triglycerides becomes enhanced in HLP type IIa. Treatment with CD that primarily may inhibit bile acid biosynthesis results in a decreased production of plasma triglycerides both in HLP type IIa and IV

INDIVIDUAL SERUM BILE ACIDS (VI)

Method. Mass fragmentography (combined gas chromatography – mass spectrometry) was used for the determination of C CD and D in serum. [2 2 3 4 4 H] C was used as internal standard for C and [11 11 12 H,] D as internal standard for both CD and D The bile acids were hydrolyzed, extracted, methylated and converted to trimethylsilyl ethers In the mass fragmentographic assay C was quantitated from the ratio between the tracing at m/e 368 (M 3 × 90 of derivative of unlabelled C) and that at m/e 3 (M 3 × 90 of derivative of deuterium labelled C) Accordingly D was antitated from the ratio between the tracing at m/e 370 (M 2 × 90 of deriva

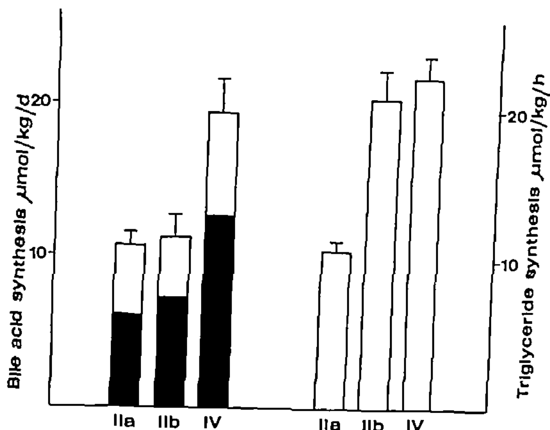


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Conclusions Under basal conditions in patients with HLP type IIa or IV the rate of degradation of cholesterol to bile acids appears to reflect the rate of plasma triglyceride formation. Upon stimulation of bile acid production by a bile acid sequestering agent, the production of plasma triglycerides becomes enhanced in HLP type IIa Treatment with CD that primarily may inhibit bile acid biosynthesis results in a decreased production of plasma triglycerides both in HLP type IIa and IV

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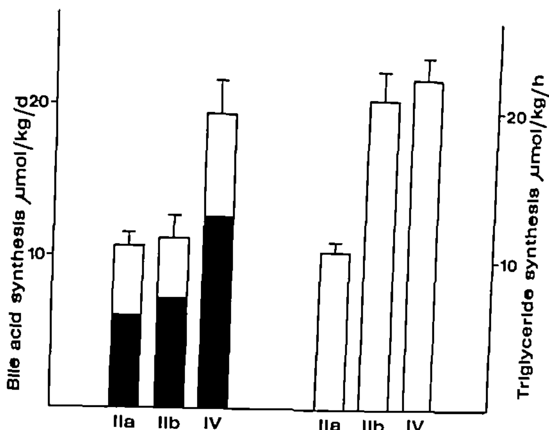


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Conclusions. A method was developed for assay of individual bile acids in serum using mass fragmentography The serum concentration of C is decreased in type IIa and IIb HLP but within normal limits in HLP type IV Serum levels of C reflect C pool size in controls and type IIa HLP

ENTEROHEPATIC CIRCULATION OF INDIVIDUAL BILE ACIDS (V VII, VIII)

Absorption of bile acids in the proximal small intestine (V) In 22 subjects (5 controls 8 with type IIa and 9 with type IV HLP) samples of intestinal content were drawn through a double-lumen tube, with the upper hole located at the ligament of Treitz (80 cm from the teeth) and the lower one 100 cm further down. The relative bile acid composition (C CD:D %) in the samples drawn from the 80 cm level averaged 37 31 32% The corresponding figures in samples from the 180 cm level were 43:27.30 Thus, the ratio between C and CD was considerably higher 1 73 ± 0 16 in the samples from the 180 cm level compared to those drawn at the 80 cm level 1 24 ± 0 08 Disregarding the uptake of C the mean absorption of C and CD along the segment studied was estimated to 28 and 23% respectively

Portal venous and systemic serum bile acids (VII) Portal venous serum concentration of C averaged 6 14 ± 1 20 µmol/l in 10 subjects undergoing elective cholecystectomy The CD concentration was higher (8 40 ± 1 84 µmol/l) while D showed intermediate levels (Figure 5) A highly significant difference was encountered between the bile acid concentration of portal and peripheral venous serum where C CD and D levels averaged 0 49 ± 0 16 1 55 ± 0 32 and 1 44 ± 0 57 µmol/l respectively (Figure 5) No differences were found between arterial and venous blood serum Neglecting the probable difference between peripheral and hepatic venous bile acid concentrations the fractional hepatic uptake was estimated to be 92±2% for C and 78±3% for CD.

The relative composition of bile acids in hepatic bile (C CD·D,%) was 35±5 31–2 35–6 while the contribution of CD was significantly greater in portal venous serum where the proportions were 30±3 39±2 31±5

Postprandial serum bile acids (VIII) The response in individual serum bile acid concentrations to a standardized meal was studied in five healthy subjects Fasting serum concentrations of C CD and D averaged 0 46 ± 0 06

tive of unlabelled D) and that at m/e 373 (M - 2 × 90 of deuterium-labelled D) and CD from the ratio between the corresponding tracing at m/e 370 (M 2 × 90 of derivative of unlabelled CD) and that at m/e 373 (M - 2 × 90 of derivative of deuterium-labelled D)

The standard curves obtained showed that these ratios were linear with the respective bile acid concentration up to about 20 μmol/l The accuracy of the method was tested by adding various amounts of bile acids to serum samples with known concentrations of bile acids The error in the determi nations was less than 10% for C and CD and slightly greater in the determi nation of high amounts of D The relative standard deviation (calculated from duplicate determinations of different serum extracts) was 3 4 and 7% for C CD and D respectively

Serum bile acid concentrations In the control subjects (n = 21) the concen tration of C averaged 0 47 ± 0 06 μmol/l while those of CD (1 45 ± 0 15 μmol/l) and of D (1 12 ± 0 11 μmol/l) were significantly higher In samples drawn at an interval of 15-30 min in the fasting state the coefficient of variation in the determination of C CD and D was 4 3 and 3% respectively The corresponding coefficients in samples drawn in the fasting state one week – three months apart were 13 21 and 35%

In type IIa HLP (n = 32) the serum levels of C (0 30 ± 0 03 μmol/l) and CD (1 06 ± 0 11 μmol/l) were significantly lower than those encountered in the controls A similar pattern was seen in patients with type IIb HLP (n = 10) whereas those with HLP type IV (n = 32) did not differ from the normo lipidaemic controls Bile acid concentration did not correlate to sex, body weight or serum lipid levels The serum concentration of D in patients with GBD was higher than that in the total series of patients

Relation to bile acid kinetics Altogether 42 subjects were included in this study The serum level of C correlated positively to the C pool size in the controls ($r = +0\ 93$ $P < 0\ 025$) and in the patients with type IIa HLP ($r = +0\ 66$ $P < 0\ 005$) No significant correlation was seen in type IV HLP although the patients with this disorder appeared to form two subgroups In about half of the patients the serum concentration seemed to correlate with the pool size The serum concentration of CD did not show any correlation to the CD pool size in any of the subgroups Bile acid formation did not relate to serum levels

GENERAL DISCUSSION

The importance of the enterohepatic circulation of bile acids in the regulation of lipid metabolism is well documented (for review 32 58) The biosynthesis of the primary bile acids is controlled by the amounts of bile acids returning to the liver in the portal vein (feed back inhibition) The fractional turnover rate of C is in general higher than that of CD (37) The current investigation indicates that these two primary bile acids also differ with regard to the site of their intestinal resorption. This difference, which results in a slower enterohepatic circulation of the trihydroxy cholanoic acid C than of the dihydroxy cholanoic acid CD may have some implications physiological as well as methodological. CD in contrast to C appears to suppress the hepatic secretion of cholesterol (3 69 70) Moreover in numerous studies dealing with bile acid kinetics the ratio between the concentrations of individual bile acids in the bile has been used as an index of the relation between the sizes of their pools Such indices and data recorded for the pool size of one bile acid have been used in the calculation of the total amount of bile acids in the enterohepatic circuit. On the basis of the present findings it appears beyond doubt that a proper determination of the total bile acid pool size requires determinations of the pool sizes of the individual bile acids

The bile acids reaching the liver in the portal vein are cleared from the circulation very rapidly C more efficiently than CD and D The concentration of bile acids in peripheral blood serum is thus very low and accounts for only a minute part of the total pool. The easy accessibility of serum bile acids has made them a subject of much interest, particularly since radioimmunoassay techniques were introduced (101) The level of an individual bile acid in serum is mainly determined by the momentary balance between input from intestinal absorption and the output due to hepatic clearance (cf 58) Elevated concentrations of bile acids in serum in hepatocellular disease has been recognized since long (26 98) but the factors determining the levels in fasting healthy man have not been subject to much study

In the present investigation, the concentration of CD in peripheral venous serum was about three times that of C a consequence both of the more rapid enterohepatic circulation and of the less efficent clearance. The concentration of C in serum was related to the pool size of C both in controls and in the patients with type IIa HLP Thus the lower serum level of C

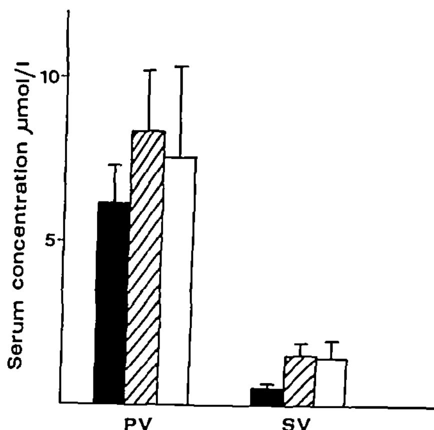


Figure 5 Serum concentration of bile acids
(■ cholic acid ▨ chenodeoxycholic acid, □ deoxycholic acid µmol/l) in portal (PV) and systemic vein (SV)

1 06 ± 0 11 and 1 22 ± 0 21 µmol/l respectively A significant rise in serum CD and D was seen already 30 min after the meal with a CD level twice that seen in the basal state C showed a significant increase in serum concentration after 60 min The peak levels were seen after 90 min for all bile acids with the concentration of C averaging 1 01 ± 0 07 that of CD 3 04 ± 0 23 and that of D 2 24 ± 0 26 µmol/l After 150 min, the C concentration had returned to basal level whereas the CD concentration was still significantly higher than basal.

Conclusions The serum level of C is normally lower than that of CD This finding may have a dual explanation. Firstly CD circulates through the enterohepatic system at a higher rate than C Secondly the hepatic clearance of C exceeds that of CD

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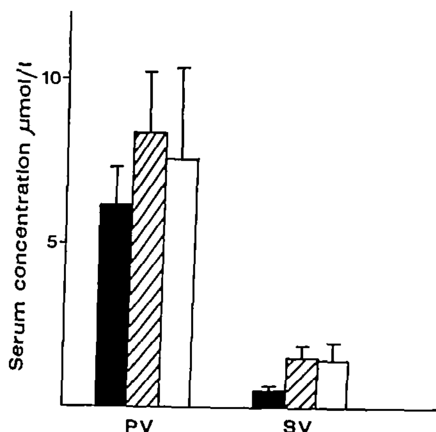


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cholestyramine increases bile acid synthesis while excretion as faecal neut ral steroids is unaffected (74) Experiments in the rat have demonstrated that de novo formed cholesterol is preferred for the synthesis of bile acids (11 31) especially for that of C (76) Preliminary data from our laboratory suggest that this also applies to man (8) If so the synthesis of C would appear to be an index' of the hepatic cholesterogenesis VLDL cholesterol and bile acids (especially C) may thus in part originate from the same pool of newly-synthesized cholesterol. This hypothesis is further supported by the finding that stimulation as well as suppression of the bile acid formation is associated with reciprocal changes in the plasma triglyceride turnover

The finding of an elevated cholesterol saturation in the bile and an increased occurence of GBD in the patients with type IV HLP is of major interest. This indicates that GBD may be the manifestation of a more generalized metabolic disorder The parallel changes in VLDL concentration (75) and biliary cholesterol saturation (9) in patients with type IV HLP during treatment with CD attract further attention to the possible role of a deranged lipoprotein metabolism as a factor in the evolution of supersaturated bile.

encountered in the latter group reflects the reduced size of the C pool de monstrated in previous work (37) In HLP type IV however large pool sizes of C were not associated with elevated serum levels of this bile acid. Dis regarding the possibility of an increased clearance, the present evidence does suggest a reduced efficacy for the uptake of C in some patients with type IV HLP In accordance with this concept a decreased capacity to re tain orally administered C in these patients has been observed (39)

The elimination of cholesterol as bile acids is within the normal range in HLP type IIa and type IIb but above normal in about 50% of the patients with the type IV lipoprotein pattern (37) The various types of HLP also differ with regard to the formation of individual bile acids the production of C being subnormal in HLP type IIa and type IIb but abnormally high in HLP type IV The present study demonstrates that the amount of cholesterol ex creted as bile acids roughly reflects the rate of cholesterol biosynthesis. In agreement with the former observation the activity of the rate-determin ing step in cholesterol biosynthesis HMG CoA reductase has recently been demonstrated to be about twice as high in the liver from patients with type IV HLP as compared to those with normal lipids (5)

As a general finding HLP type IV turns out to be heterogeneous with re gard to defects in the metabolism of cholesterol and bile acids Similarly a heterogeneous pattern has been recorded in studies of lipoprotein (apo B) and triglyceride kinetics Under basal conditions the formation of bile acids correlates with the production of plasma triglycerides i e VLDL Further support for the concept of a linkage between the formation of VLDL triglycerides and that of cholesterol and bile acids is gained from studies on the effects of treatment with hypolipidaemic drugs or diets The reduced triglyceride synthesis induced by weight reduction (85) or by the administ ration of clofibrate (83) or nicotinic acid (84) to patients with the type IV lipoprotein pattern is accompanied by a decreased formation of bile acids (36 37 42) The increased triglyceride formation during feeding with a high carbohydrate diet (79) appears to be linked to an increased degradation of cholesterol to bile acids (7) There is also some evidence that the turnover of plasma triglycerides correlates with that of plasma cholesteryl esters and presumably to hepatic cholesterol biosynthesis (66)

It has been suggested that at least two hepatic cholesterol pools are pre sent one anabolic' for lipoprotein synthesis and one catabolic derived from lipoprotein breakdown and used for elimination as bile acids and neut- ral steroids (104 105) However several lines of evidence suggest that the hepatic pool of cholesterol available for bile acid synthesis is not identical with that of cholesterol excreted into the bile Accordingly the administration of

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encountered in the latter group reflects the reduced size of the C pool demonstrated in previous work (37) In HLP type IV however large pool sizes of C were not associated with elevated serum levels of this bile acid. Disregarding the possibility of an increased clearance the present evidence does suggest a reduced efficacy for the uptake of C in some patients with type IV HLP In accordance with this concept a decreased capacity to retain orally administered C in these patients has been observed (39)

The elimination of cholesterol as bile acids is within the normal range in HLP type IIa and type IIb but above normal in about 50% of the patients with the type IV lipoprotein pattern (37) The various types of HLP also differ with regard to the formation of individual bile acids the production of C being subnormal in HLP type IIa and type IIb but abnormally high in HLP type IV The present study demonstrates that the amount of cholesterol excreted as bile acids roughly reflects the rate of cholesterol biosynthesis. In agreement with the former observation the activity of the rate-determining step in cholesterol biosynthesis HMG CoA reductase has recently been demonstrated to be about twice as high in the liver from patients with type IV HLP as compared to those with normal lipids (5)

As a general finding HLP type IV turns out to be heterogeneous with regard to defects in the metabolism of cholesterol and bile acids Similarly a heterogeneous pattern has been recorded in studies of lipoprotein (apo B) and triglyceride kinetics Under basal conditions the formation of bile acids correlates with the production of plasma triglycerides i e VLDL Further support for the concept of a linkage between the formation of VLDL triglycerides and that of cholesterol and bile acids is gained from studies on the effects of treatment with hypolipidaemic drugs or diets The reduced triglyceride synthesis induced by weight reduction (85) or by the administration of clofibrate (83) or nicotinic acid (64) to patients with the type IV lipoprotein pattern is accompanied by a decreased formation of bile acids (36 37 42) The increased triglyceride formation during feeding with a high carbohydrate diet (79) appears to be linked to an increased degradation of cholesterol to bile acids (7) There is also some evidence that the turnover of plasma triglycerides correlates with that of plasma cholesteryl esters and presumably to hepatic cholesterol biosynthesis (66)

It has been suggested that at least two hepatic cholesterol pools are present one 'anabolic for lipoprotein synthesis and one catabolic derived from lipoprotein breakdown and used for elimination as bile acids and neutral steroids (104 105) However several lines of evidence suggest that the hepatic pool of cholesterol available for bile acid synthesis is not identical with that of cholesterol excreted into the bile Accordingly the administration of

respectively Lower values were seen in patients with type IIa and type IIb HLP

In controls and in patients with type IIa HLP the serum concentration of C correlated to C pool size No such relationship was seen in HLP type IV

4 The ratio between C and CD concentrations were determined in intestinal aspirates from different levels of the proximal small intestine. There was an increased C/CD ratio in samples from distal parts consistent with CD absorption of about 30% along the segment studied.

Portal venous serum was analyzed for bile acids and concentrations six to ten times those of peripheral serum were observed. The fractional hepatic uptake was estimated to be circa 90% for C and about 80% for CD and D

The serum bile acid levels were followed during a standardized meal CD (and D) showed an earlier and more prolonged rise in serum concentration compared with C The maximum level was reached after about 60 min for all three acids

GENERAL SUMMARY

1 Bile acid kinetics (isotope dilution) faecal neutral steroid elimination (gas chromatography) and cholesterol intake were determined under basal conditions in 69 normo- and hyperlipoproteinaemic subjects The net steroid 'balance calculated as bile acid synthesis + faecal neutral steroid excretion – dietary intake averaged 1 6 mmol/day in controls and in patients with type IIa and IIb HLP Type IV HLP was frequently associated with an increased 'balance mean 3 5 mmol/day mainly due to an increased production of bile acids

In altogether 210 patients with HLP the incidence of GBD was deter mined and compared to the findings in three age-matched necropsy series An increased occurence of GBD was seen in patients with type IV lipoprotein pattern The biliary lipid composition was analyzed in patients with HLP Both type IIb and type IV HLP displayed an increas ed saturation of cholesterol in the bile compared to type IIa HLP

2 Bile acid kinetics (isotope dilution) and plasma endogenous triglyceride turnover (^{3}H glycerol technique) were determined in patients with type IIa IIb and IV HLP under basal conditions In agreement with previous studies the formation of C was higher in type IV than in type IIa or IIb HLP A correlation between the formation of bile acids (especially that of C) and the synthesis of plasma triglycerides was present in type IIa and type IV HLP

Triglyceride kinetics were determined before and during induction of an increased bile acid formation by cholestyramine treatment. In pati ents with type IIa HLP plasma triglyceride formation and fractional turnover rate increased while no consistent changes were seen in type IV HLP

A similar analysis of triglyceride kinetics before and during suppres sion of bile acid synthesis by CD feeding showed a decreased formation of triglycerides both in type IIa and type IV HLP

3 A mass fragmentographic technique for determination of serum bile acids was developed and evaluated The fasting concentrations in serum of C CD and D averaged 0 47 ± 0 06 1 45 ± 0 16 and 1 12 ± 0 11 μmol/l

respectively Lower values were seen in patients with type IIa and type IIb HLP

In controls and in patients with type IIa HLP the serum concentration of C correlated to C pool size No such relationship was seen in HLP type IV

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REFERENCES

1 Adams P W Kissebah, A H. Harrigan, P Stokes, T Wynn, V The kinetics of plasma free fatty acid and triglyceride transport in patients with idiopathic hypertriglyceridaemia and their relation to carbohydrate metabolism. Eur J Clin. Invest. 4 149 1974

2. Admirand, W H. Small, D.M. The physico-chemical basis of cholesterol gallstone formation in man. J Clin. Invest. 47 1043 1968

3 Adler R.D Bennion, L.J Duane, W C Grundy S.M. Effects of low dose chenodeoxycholic acid feeding on biliary lipid metabolism Gastroenterology 68 326 1975

4 Ahlberg, J Angelin, B Björkhem, I. Einarsson, K. Leijd, B Manuscript in preparation.

5 Ahlberg J Angelin, B. Björkhem, I. Einarsson, K. Leijd, B Manuscript in preparation.

6 Ahlberg, J Angelin, B Einarsson, K. Leijd, B Manuscript in preparation.

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9 Angelin, B Einarsson, K. Leijd, B To be published.

10 Balasubramaniam, S. Goldstein, J L. Faust, J R. Brown, M.S. Evidence for regulation of 3-hydroxy 3 methylglutaryl coenzyme A reductase activity and cholesterol synthesis in nonhepatic tissues of rat. Proc Nat, Acad. Sci. USA 73 2564 1976

11 Balasubramaniam, S. Mitropoulos, K.A. Myant, N B Evidence for the compartmentation of cholesterol in rat liver microsomes Eur J Biochem. 34 77 1973

12 Beaumont, J L. Carlson, L.A. Cooper G R., Fejfar Z. Fredrickson, D S. Strasser T Classification of hyperlipidaemias and hyperlipoproteinaemias Bull. WHO 43 891 1970

13 Bennion, L.J Ginsberg R.L. Garnick, M.B Effects of oral contraceptives on the gallbladder bile of normal women. N Engl. J. Med. 294 189 1976

14 Bennion, L.J Grundy S.M. Effects of obesity on caloric intake on biliary lipid metabolism in man. J Clin Invest. 56 996 1975

15 Bhattacharyya, A.K. Connor W E. Spector A.A. Excretion of sterols from the skin of normal and hypercholesterolemic humans. Implication for sterol balance studies. J. Clin. Invest. 51 2060 1972

16 Boberg J Carlson, L A., Freyschuss U Lassers B W Wahlqvist M. L Splanchnic secretion rates of plasma triglycerides and total and splanchnic turnover of plasma free fatty acids in men with normo and hypertriglyceridaemia. Eur J Clin. Invest. 2 454 1972

17 Bolzano K., Sandhofer F Sailer S Braunsteiner H. Studies on cholesterol turnover in hypercholesterolemic subjects Horm Metabol Res 5 444 1973

18 Borgström B Quantification of cholesterol absorption in man by fecal analysis after the feeding of a single isotope labelled meal J Lipid Res 10 331 1969

19 Boston Collaborative Drug Surveillance Programme Oral contraceptives and venous thromboembolic disease surgically confirmed gallbladder disease and breast tumors Lancet 1 1399 1973

20 Brown, M S Goldstein J L Expression of the familial hypercholes terolemia gene in heterozygotes Mechanism for a dominant disorder in man Science 185 61 1974

21 Brown M S Goldstein, J L. Regulation of the activity of the low den sity lipoprotein receptor in human fibroblasts Cell 6 307 1975

22 Brown, M. S Goldstein, J L. Familial hypercholesterolemia Genetic biochemical and pathophysiological considerations Adv Intern Med 20 273 1975

23 Brown, M. S Goldstein, J L Familial hypercholesterolemia A gene tic defect in the low-density lipoprotein receptor N Engl J Med. 294 1386 1976

24 Brown M. S Goldstein, J L. Receptor mediated control of cholesterol metabolism Science 191 150 1976

25 Brunzell J D Hazzard, W R. Porte D Jr Bierman, E L. Evidence for a common saturable triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J Clin. Invest. 52 1578 1973

26 Carey J B Jr Bile acids in the serum of jaundiced patients Gastro enterology 41 285 1961

27 Carlson, L A. Boberg J Högstedt, B Some physiological and clinic al implications of lipid mobilization from adipose tissue In Handbook of physiology, sect V Adipose tissue (Ed A E Renold G F Cahill Jr) p 625 Washington D C American Physiological Society 1965

28 Chobanian, A V Burrows B A. Hollander W Body cholesterol metabolism in man. II. Measurement of the body cholesterol miscible pool and turnover rate J Clin. Invest 41 1738 1962

29 The Coronary Drug Project Clofibrate and niacin in coronary heart disease JAMA 231 360 1975

30 Coyne M. J Bonorris G G Goldstein L. L Schoenfield L. J Effect of chenodeoxycholic acid and phenobarbital on the rate limiting enzymes of hepatic cholesterol and bile acid synthesis in patients with gallstones J Lab Clin. Med 87 281 1976

31 Cronholm T Burlingame, A. L., Sjövall, J Utilization of the carbon and hydrogen atoms of ethanol in the biosynthesis of steroids and bile acids Eur J Biochem 49 497 1974

32 Danielsson, H. Sjövall J Bile acid metabolism. Annu Rev Biochem 44 233 1975

33 Dietschy J M. The role of bile salts in controlling the rate of intestinal cholesterogenesis Gastroenterology 47 286 1968

34 Dietschy J M. Wilson, J D. Regulation of cholesterol metabolism N Engl J Med. 282 1128 1179 1241 1970

35 Eaton, R. P Synthesis of plasma triglycerides in endogenous hypertriglyceridemia J. Lipid Res 12 491 1971

36 Einarsson, K. Hellström K. Kallner M. The effect of clofibrate on the elimination of cholesterol as bile acids in patients with hyperlipoproteinaemia type II and IV Eur. J Clin. Invest 3 345 1973

37 Einarsson, K. Hellström K. Kallner M. Bile acid kinetics in relation to sex, serum lipids, body weights and gallbladder disease in patients with various types of hyperlipoproteinemia. J. Clin. Invest. 54 1301 1974

38 Einarsson, K. Hellström K. Kallner M. Randomly tritium labelled chenodeoxycholic acid as tracer in the determination of bile acid turn over Clin. Chim. Acta 56 235 1974

39 Einarsson, K. Hellström K. Kallner M. On the effect of cholic acid feeding on bile acid kinetics and neutral fecal steroid excretion in hyper lipoproteinemia type II and IV Metabolism 23 863 1974

40 Einarsson, K., Hellström, K. Kallner M. The effect of cholestyramine on the elimination of cholesterol as bile acids in patients with hyperlipoproteinaemia type II and IV Eur J Clin. Invest. 4 405 1974

41 Einarsson, K. Hellström, K. Kallner M. Gallbladder disease in hyperlipoproteinemia Lancet I. 484 1975

42 Einarsson, K. Hellström, K. Leijd, B Bile acid kinetics and steroid balance during nicotinic acid therapy in patients with hyperlipoproteinemia type II and IV J Lab. Clin. Med. In press 1977

43 Eisenberg S. Levy R. I. Lipoproteins and lipoprotein metabolism In: Hypolipidemic agents (Ed. D Kritchevsky) p. 191 Berlin Heidelberg New York Springer Verlag 1975

44 Eneroth, P Hellström K. Ryhage R. Identification and quantification of neutral fecal steroids by gas liquid chromatography and mass spectrometry Studies of human excretion during two dietary regimens J. Lipid Res 5 245 1964

45 Faergeman, O. Havel, R. J Metabolism of cholesterol esters of rat very low density lipoproteins J Clin. Invest 55 1210 1975

46 Farquhar J W Gross R. C., Wagner R. M. Reaven, G M. Validation of an incompletely coupled two-compartment nonrecycling catenary model for turnover of liver and plasma triglyceride in ...

16 Boberg J Carlson, L A. Froyschuss U Lassers B W Wahlqvist, M L Splanchnic secretion rates of plasma triglycerides and total and splanchnic turnover of plasma free fatty acids in men with normo and hypertriglyceridaemia Eur J Clin Invest. 2 454 1972

17 Bolzano K. Sandhofer F Sailer S Braunsteiner H. Studies on cholesterol turnover in hypercholesterolemic subjects Horm Metabol Res 5 444 1973

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20 Brown M S. Goldstein J L Expression of the familial hypercholesterolemia gene in heterozygotes Mechanism for a dominant disorder in man Science 185 61 1974

21 Brown, M. S Goldstein J L. Regulation of the activity of the low density lipoprotein receptor in human fibroblasts Cell 6 307 1975

22 Brown M. S Goldstein, J L. Familial hypercholesterolemia Genetic biochemical and pathophysiological considerations Adv Intern Med 20 273 1975

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25 Brunzell, J D Hazzard, W R. Porte, D Jr Bierman E L. Evidence for a common saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man J Clin Invest. 52 1578 1973

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27 Carlson, L A. Boberg J Högstedt, B Some physiological and clinical implications of lipid mobilization from adipose tissue In Handbook of physiology, sect. V Adipose tissue (Ed A E Renold G F Cahill, Jr) p 625 Washington D C American Physiological Society 1965

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63 Kekki, M. Nikkilä, E.A. Turnover of plasma total and very low density lipoprotein triglyceride in man. Scand. J. Clin. Lab Invest. 35 171 1975

64 Klasebah, A.H. Adams, P W Harrigan, P Wynn, V The mechanism of action of clofibrate and tetranicotinoylfructose (Bradilan) on the kinetics of plasma free fatty acid and triglyceride transport in type IV and type V hypertriglyceridaemia. Eur J. Clin. Invest 4 163 1974

65 Krauss R.M. Levy R.I. Fredrickson, D.S. Selective measurements of two lipase activities in postheparin plasma from normal subjects and patients with hyperlipoproteinemia. J. Clin. Invest. 54 1107 1974

66 Kudchodkar, B.J Sodhi, H.S. Turnover of plasma cholesteryl esters and its relationship to other parameters of lipid metabolism in man. Eur J. Clin. Invest. 6 285 1976

67 Kudchodkar B.J Sodhi, H.S. Horlick, L. Absorption of dietary cholesterol in man. Metabolism 22 155 1973

68 Langer, T Strober W Levy R.I. The metabolism of low density lipoprotein in familial type II hyperlipoproteinemia. J. Clin. Invest. 51 1528 1972

69 LaRusso, N.F , Hoffman, N.E. Hofmann, A.F Northfield, T C. Thistle J L. Effect of primary bile acid ingestion on bile acid metabolism and biliary lipid secretion in gallstone patients Gastroenterology 69 1301 1975.

70 Lindblad, L. The significance of bile acids for bile flow and biliary lipid secretion in man. Thesis, Göteborg 1976

71 Lindstedt, S. Turnover of cholic acid in man. Acta Physiol. Scand. 40 1 1957

72 Lindström C H. Frequency of gallstone disease in a well defined Swedish population. A prospective necropsy study in Malmö Scand.J Gastroent. In press 1977

73 Miettinen, T A. Detection of changes in human cholesterol metabolism. Ann. Clin. Res 2 300 1970

74 Miettinen, T A. Bile acid metabolism. In. Hypolipidemic agents (Ed. D Kritchevsky) p.109 Berlin Springer Verlag 1975

75 Miller N E. Nestel, P J Triglyceride-lowering effect of chenodeoxycholic acid in patients with endogenous hypertriglyceridaemia. Lancet II. 929 1974

76 Mitropoulos, K.A. Myant, N B. Gibbons, G F Balasubramaniam, S. Reeves B. Cholesterol precursor pools for the synthesis of cholic and chenodeoxycholic acids in rats J. Biol. Chem. 249 6052 1974

77 Morrisett, J D Jackson, R.L. Gotto, A.M. Lipoproteins structure and function. Annu. Rev. Biochem. 44 183 1975

78 Motulsky, A.G. Current concepts in genetics The genetic hyperlipidemias N. Engl. J Med 294 823 1976

47 Felts, J M Rudel, L L. Mechanisms of hyperlipidemia. In Hypolipidemic agents (Ed. D Kritchevsky) p 151 Berlin Springer Verlag 1975

48 Fredrickson, D S Levy, R L Familial hyperlipoproteinemia In The metabolic basis of inherited disease (Eds J B Stanbury J B Wyngaarden D S Fredrickson) p 545 New York McGraw Hill Book Co 1972

49 Fredrickson, D S. Levy, R L Lees R S. Fat transport in lipoproteins – an integrated approach to mechanisms and disorders N Engl J Med. 276 34 94 148 215 273 1967

50 Gangl A. Ockner, R K. Intestinal metabolism of lipids and lipoproteins Gastroenterology 68 167, 1975

51 Goldstein, J L., Schrott, H. G Hazzard, W R. Bierman, E. L Motulsky, A. G Hyperlipidemia in coronary heart disease II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder combined hyperlipidemia. J Clin. Invest. 52 1544 1973

52 Grundy, S. M. Ahrens E H. Salen, G Schreibman, P Cholesterol metabolism in patients with hyperlipidemia J Lipid Res 13 531 1972

53 Hamprecht, B Roscher R. Waltinger G Wüssler C Influence of bile acid on the activity of rat liver 3 hydroxy-3-methylglutaryl coenzyme A reductase Effect of cholic acid in lymph fistula rats Eur J Biochem 18 15 1971

54 Havel R. J Pathogenesis differentiation and management of hypertriglyceridemia. Adv Intern Med 15 117 1969

55 Havel, R. J Metabolism of plasma triglycerides In Proceedings II. International Symposium on Atherosclerosis (Ed. R. J Jones) p 209 New York Springer-Verlag 1970

56 Havel R. J Kane, J P Balasse E O. Segel, N Basso, L. V Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans J Clin. Invest 49 2017 1970

57 Hegardt, F G Dam H. The solubility of cholesterol in aqueous solutions of bile salts and lecithin. Z Ernährungsw 10 223 1971

58 Hofmann, A. F The enterohepatic circulation of bile acids in man Adv Intern. Med. 21 501 1976

59 Holzbach, R. T March M., Olszewski, M. Holan, K. Cholesterol solubility in bile evidence that supersaturated bile is frequent in healthy man J Clin. Invest. 52 1467 1973

60 Jackson, R. L. Morrisett, J D Gotto, A. M. Jr Lipoprotein structure and metabolism Physiol Rev 56 259 1976

61 Kallner M. The effect of chenodeoxycholic acid feeding on bile acid kinetics and fecal neutral steroid excretion in patients with hyperlipoproteinemia types II and IV J Lab Clin. Med 86 595 1975

62 Kaye, J P Galton, D J Triglyceride-production rates in patients with type IV hypertriglyceridaemia. Lancet 1 1005 1975

95 Sandberg D.H. Sjövall, J Sjövall, K. Turner D A. Measurement of human serum bile acids by gas liquid chromatography J. Lipid Res 6 182 1965

96 Shefer S. Hauser S., Lapar V Mosbach, E.H. Regulatory effects of dietary sterols and bile acids on rat intestinal HMG CoA reductase J. Lipid Res 14 400 1973

97 Shefer S. Hauser S., Lapar V Mosbach, E.H. Regulatory effects of sterols and bile acids on hepatic 3 hydroxy 3 methylglutaryl CoA reductase and 7α hydroxylase in the rat J. Lipid Res 14 573 1973

98 Sherlock, S. Walshe, V Blood cholates in normal subjects and in liver disease. Clin Sci. 6 223 1948

99 Sigurdsson, G Nicoll, A., Lewis B The metabolism of low density lipoprotein in endogenous hypertriglyceridaemia. Eur. J Clin. Invest. 8 151 1978

100 Sigurdsson, G Nicoll, A. Lewis, B. Metabolism of very low density lipoproteins in hyperlipidaemia studies of apolipoprotein B kinetics in man. Eur. J Clin. Invest. 6 167 1976

101 Simmonds, W J Korman, M.G, Go V L.W Hofmann, A.F Radio immunoassay of conjugated cholyl bile acids in serum Gastroenterology 65 705 1973

102 Snedecor G W Cochran, W G Statistical methods 6th edition. Iowa State University Press Ames 10 1974

103 Sniderman, A.D., Carew T E. Chandler J G Steinberg, D Para doxical increase in rate of catabolism of low-density lipoproteins after hepatectomy Science 183 526 1974

104 Sodhi, H.S. Cholesterol metabolism in man. In. Hypolipidemic agents (Ed. D Kritchevsky) p 29 Berlin Heidelberg New York, Springer Verlag 1975

105 Sodhi, H.S. Kudchodkar B J Correlating metabolism of plasma and tissue cholesterol with that of plasma lipoproteins Lancet 1 513 1973

106 Spritz, W Ahrens, E.H. Grundy S.M. Sterol balance in man as plasma cholesterol concentrations are altered by exchanges of dietary fats J Clin. Invest. 44 1482 1965

107 Sternby, N H. Atherosclerosis in a defined population. An autopsy survey in Malmö Sweden. Acta Path. Microbiol Scand. Suppl. 194 1968.

108 Thomas P J Hofmann, A.F A simple calculation of the lithogenic index of bile expressing biliary lipid composition on rectangular coor dinates Gastroenterology 65 698 1973

109 Vlahcevic Z.R. Miller, J R., Farrar J T Swell, L. Kinetics and pool sizes of primary bile acids in man. Gastroenterology 61 85 1971

79 Nestel, P J Triglyceride turnover in man. Effects of dietary carbo hydrate Prog. Biochem. Pharmacol 8 125 1973

80 Nestel P J Whyte, H. M. Goodman, D S. Distribution and turnover of cholesterol in humans J Clin. Invest 48 982, 1969

81 Nikkilä, E A. Aro A. Family study of serum lipids and lipoproteins in coronary heart-disease Lancet 1 954, 1973

82 Nikkilä, E A. Kekki, M. Polymorphism of plasma triglyceride kinetics in normal human adult subjects Acta Med Scand. 190 49 1971

83 Nikkilä, E. A Kekki M. Plasma endogenous triglyceride transport in hypertriglyceridaemia and effect of a hypolipidaemic drug (SU 13437) Eur J Clin. Invest 2 231 1972

84 *Olefsky J Farquhar J W Reaven, G M.* Sex difference in the kine tics of triglyceride metabolism in normal and hypertriglyceridaemic human subjects Eur J Clin. Invest 4 121 1974

85 Olefsky J , Reaven, G M. , Farquhar J W Effects of weight reduction on obesity Studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects J Clin. Invest 53 64 1974

86 Pertsemlidis D Panveliwalla, D Ahrens E. H. Effects of clofibrate and of an estrogen-progestin combination on fasting biliary lipids and cholic acid kinetics in man. Gastroenterology 66 565 1974

87 Porte, D. Jr Bierman E L The effect of heparin infusion on plasma triglyceride in vivo and in vitro with a method for calculating triglyceride turnover J Lab Clin. Med 73 631 1969

88 Quarfordt, S H. Frank, A. Shames D M Berman, M. Steinberg D Very low density lipoprotein triglyceride transport in type IV hyperlipo proteinemia and the effects of carbohydrate rich diets J Clin. Invest 49 2281 1970

89 Quintão E , Grundy S M , Ahrens E. H. Jr *Effects of dietary cho* lesterol on the regulation of total body cholesterol in man. J Lipid Res 12 233 1971

90 Reaven, G M Hill, D B Gross R. C Farquhar J W Kinetics of triglyceride turnover of very low density lipoproteins of human plasma J Clin Invest 44 1826 1965

91 Redinger, R. N Small, D M. Bile composition, bile salt metabolism and gallstones Arch Intern Med 130 618 1972

92 Robinson D S The function of the plasma triglycerides in fatty acid transport Comp Biochem 18 51 1970

93 Rodwell V W , Nordstrom, J L Mitschelen, J J Regulation of HMG-CoA reductase. Adv Lipid Res 14 1 1976

94 Sailer S Sandhofer F Braunsteiner H. Umsatzraten für freie Fettsäuren und Triglyceride im Plasma bei essentieller Hyperlipämie Klin Wochenschr 44 1032 1966

110 Walldius G Fatty acid incorporation into human adipose tissue in hypertriglyceridaemia. Methodological clinical and experimental studies Acta Med Scand. Suppl 591 1976

111 Weis H.J , Dietschy J M. Failure of bile acids to control hepatic cholesterogenesis Evidence for endogenous cholesterol feedback. J Clin Invest 48 2398 1969

112 Zahor Z Sternby N H. Kagan, A., Uemura, K. Vanecik, R., Vichert, A.M. Frequency of cholelithiasis in Prague and Malmö An autopsy study Scand. J Gastroent. 9 3 1974

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and Roentgenology III of the University of Gothenburg
the Gothenburg Medical Services Administration and the
Gothenburg Administration of Social Services

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SEVENTY-YEAR-OLD PEOPLE IN GOTHENBURG
A POPULATION STUDY IN AN INDUSTRIALIZED SWEDISH CITY
II GENERAL PRESENTATION OF SOCIAL AND MEDICAL CONDITIONS

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ABSTRACT

The prospective longitudinal population study of elderly individuals in Gothenburg started in 1971/72 with an investigation of a representative sample (about 3/10) of the 70 year-olds This wide population study concerns the nature and manifestations of normal ageing processes the incidence and prevalence of disease at higher ages and the occurrence and the nature of infirmity in old age This paper is a general description of some of the social and medical observations obtained during the first study of the probands and concerns migration in the population housing dwelling conditions mobility

and transportations social contacts need of help results of the general othological ophthalmological psychiatric psychological and odontological examinations as well as of certain laboratory analyses The results showed that underdiagnosis was common in this age group i e that *previously unknown disease often* was present The results also indicate that overdiagnosis is rather common due to the fact that the border zone between normal ageing and disease is only a very vague presentiment in the higher age groups More advanced handicaps were rather uncommon and only about 3 per cent of the 70-year-olds suffered from handicaps or diseases to such an extent that care within institutions was necessary The 70-year-olds rather *commonly are living under social conditions* that from a medical point of view might be subjected to critizism It should however also be emphasized that a majority of the 70-year-olds in Gothenburg were living a very comfortable life in rather good physical and mental condition

INTRODUCTION

There are obvious and urgent needs for more knowledge of the nature and manifestations of normal ageing processes at higher ages as well as of the incidence and prevalence of disease at higher ages and of the occurrence and nature of infirmity in old age From a medical and sociological point of view an improvement of that knowledge is necessary for an adequate planning of service care and the prevention of disease and handicaps among the elderly

A broader knowledge in medical gerontology and geriatrics in humans necessitates epidemiological studies The prospective longitudinal population study of elderly individuals in Gothenburg the second largest city of Swedon was started in 1971/72 by an investigation of a representative sample (3/10) of the 70-year-olds (29) The first follow up started in September 1976 at the age of 75 and simultaneously another study of possible cohort-effects in a 5-year-period has been started by an investigation of another sample of individuals who were 70 years old in 1976/77

A great many specialists in different fields of gerontology and geriatrics (29) are taking part in this study More detailed presentations obtained in different research fields will be published separately The aim of this report is to introduce in a more general way the social and medical observations obtained during the first study of the probands who in 1971/72 were 70 years of age

METHODS

The design and procedure of the study analysis of observer variation and a comparison between responders (85 per cent) and non-responders (15 per cent) have been reported previously (29) This population study comprised a homecall part regarding basic personal data dwelling conditions economy social and physical communications previous migration educational level previous and any present professions need of care consumption of health care and drugs An examination at the hospital comprised broad medical examinations

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common (43 per cent) size of flat 26 per cent had one room and kitchen and the rest 3 or more rooms About one third had been living in the same house for 20 years or more but nearly as many (28 per cent) had moved into their present home during the last 5 years Eightyfour per cent of both male and female probands considered their housing standard good 11 per cent acceptable and 5 per cent bad

The general hygienic standards of the flats were usually good e g 93 per cent had a WC 90 per cent warm water and 91 per cent bathrooms thereof 83 per cent in their own apartments It should be mentioned that more probands considered the indoor temperature during wintertime too high (12 per cent) than too low (6 per cent) an observation of special interest nowadays when energy saving programmes are actual More women (25 per cent) than men (18 per cent) complained of draughts in their apartments

Seventythree per cent lived in buildings without lifts and only 6 per cent of the homes were situated on the ground floor Twelve per cent had a WC on another floor than that where the bedroom and kitchen were situated

During the visit by the nurse the probands were asked to sit down in their usual armchairs and the lighting w s measured at the level where they usually hold their books or papers when reading The intensity of illumi nation was measured upon a special surface with a entral indicator for light direction and shadow length In 72 per cent of the cases the illumination was 1 ss than 300 lu in 13 per cent less than 100 lux - in 18 per cent 300 500 lux and in only 10 15 per cent of the c ses lighting was considered to be adequate at the age of 70 The illumination was thus definitely not adjusted to the needs of the elderly Furthermore approximately 70 per cent had an inconvenient dir ction of the artificial light with risk of dazzl and inferior

dental examination psychological examination dietary interview anthropometric measurements and a body composition examination

RESULTS

Gothenburg has apparently had a relatively stable population Fiftyone per cent of the male 70-year-olds and 45 per cent of the females were born there and 11 per cent of the males and 16 per cent of the females born elsewhere had lived there for more than 50 years Only 5 per cent of the males and 7 per cent of the females had lived there less than 20 years Only 3 per cent of the 70-year-olds were born abroad and almost all of these had lived in Sweden for a sufficiently long time to obtain Swedish nationality The majority (55 per cent) of the 70-year-old population in Gothenburg were women 45 per cent of the female probands were living alone compared to only 19 per cent of the males Among males only 12 per cent were widowers Among females 42 per cent were widows Only 7 per cent of the 70-year-olds lived in extended families i e together with 3 or more persons

Housing

Almost 4 out of 5 probands were living in flats in general apartment houses and only about 10 per cent were still living in their own family houses Five per cent had moved to a housing unit for pensioners or a [illegible] Two rooms and a kitchen was the most

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contrast effect

Only 4 per cent lacked a telephone and only 1 4 per cent radio and/or TV

As their main transportation method within Gothenburg three out of four probands used the public transportation facilities and only 10 per cent had their own cars Bus or tram stops were available within 400 metres for 80 per cent of the probands About 10 per cent of the probands declared that walking was their main method of transportation Sixtyone per cent declared that they were not used to making long (≥ 2 weeks) journeys in spite of the costs of public transportation being subsidized for pensioners in Sweden Ten per cent go abroad occasionally

Twentyseven per cent owned a summer cottage and another 16 per cent used childrens *friends or rented cottages* during summer months

Social contacts

Two out of three probands had children alive and the vast majority (83 per cent) of these children were living in or close to Gothenburg Eighty per cent had met their children within the last week Fifteen per cent complained of meeting their children too seldom Only 3 women thought that they met their children too often Obviously children and grandchildren constitute the most common means of contact and only 17 per cent of those with children declared that their most common personal contact was with friends or relatives other than children One per cent had no regular personal contact at all More than one third of the probands felt that personal contact had become less common after retirement although available time had increased and one fifth declared that they had a larger circle of

friends now after retirement than before

Many foreigners feel that the average Swede is silent reserved and difficult to come into contact with Among the 70-year-olds 70 per cent declared that they never paid a visit to a neighbour and 10 per cent that they did not even talk to neighbours when they met them in the apartment house Ninety per cent declared however that they found their frequency of contacts with neighbours satisfactory

On the other hand 38 per cent of the females and 21 per cent of the males complained of a feeling of loneliness sometimes (29 per cent and 17 per cent) or often (9 per cent and 4 per cent) and 20 per cent stated that they felt themselves lonely more often at the age of 0 than they had experienced at the age of 60 Further processing of the material has shown that the majority of probands with a subjective feeling of loneliness really were lacking personal contact and that it was not unusual especially among females that one or more days passed when they did not meet or talk to anyone at all The group of 70-year olds who complained of loneliness will be studied separately with an aim to analyze from social psychological and medical points of view the reasons for this loneliness and possibilities of improving the living conditions of these people

Need_of help

A thorough study was performed on the presence of handicaps as judged from the capability of the proband to exist in his/her own environment Only 3 per cent were living in hospitals nursing homes or homes for the elderly According to our evaluation the 97 per cent living at home were able to cope but 2 per cent needed regular help with personal hygiene dressing etc

Eighteen per cent needed domicilary help Half of those needing help at home had got such help from the community services and 30 per cent had arranged help privately Only 9 per cent of those living at home but needing help got such a help from their children As mentioned earlier out of those with children 80 per cent of the children were living in Gothenburg or its surroundings and might thus from a geographical point of view have been able to assist their parents It was apparently more common that parents helped children; 20 per cent helped their children often 20 per cent sometimes and 9 per cent seldom

Ninetyfive per cent of the probands living at home were able to take a bath without any help 99 per cent managed to go to the toilet and 70 per cent were doing their laundry themselves Eleven per cent of the females and 5 per cent of the males had difficulties in rising from bed and 14 per cent and 6 per cent respectively rising from a chair without arms and 8 per cent and 5 per cent respectively of walking easily Thirteen out of 973 investigated probands used wheelchairs and only 2 individuals of those living in their own homes were bedridden Six per cent of the females and 4 per cent of the males had extra support from the community for the taxi transports or special handicap transports

Reading habits were dominated by daily newspapers 94 per cent had at least one newspaper and periodicals were procured by 67 per cent at least once a week Fortyeight per cent had no other hobby than reading Thirtyeight per cent declared that they never read a book (including the Bible) Only 8 per cent went to church every week and 44 per cent never went to church at all About 50 per cent were members of a society and 60 per cent of these probands went to society meetings at least once a month

Medical examination

The general medical examinations were performed by Dr Sture Roupe and Dr Bertil Steen and the roentgenological studies by Dr Erich Deichgräber

Eightyeight per cent of males and 85 per cent of females had been admitted to hospital sometime during their life Examples of the anamnestic life time incidences of diseases are given in Table I Thirtythree per cent of the male and 36 per cent of the female probands declared that they did not feel fit It should be noted that a great many of those who reported they felt fit later on responded in the affirmative to certain symptoms on disease when confronted with them Eighteen per cent of the males and 25 per cent of the females considered themselves to suffer from a general tiredness and had done so for at least one year

At the medical examination a great number of observations on symptoms of defineable diseases were noted More detailed descriptions of these findings will be given when the follow up of 1976/77 has been completed The present report has therefore been limited to examples on preliminary evaluations of the prevalence of certain diseases in this age group (Table I) Congestive heart failure was defined as 1) roentgenological evidence of increased heart volume plus two of the symptoms oedema dyspnoea and cyanosis or 2) all the three symptoms: oedema dyspnoea and cyanosis or 3) roentgenological evidence of pulmonary congestion or 4) roentgenological evidence of increased heart volume in the absence of systemic hypertension (23)

Early systolic murmur of an ejection character with a maximum over aorta but without lowering of the second heart sound and supposed to indicate a lowered elasticity of aorta was heard in 25 per cent of the males and 37 per cent of the females

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	Males	Females
Constipation laxative consumption	13	21
Gall stone anamnestic	14	29
Inguinal hernia	29	0
Mammary carcinoma	-	3
Urinary incontinence		
at cough and/or laughter	6	44
at night	2	1
Catheter or uridome	1	1
Bacteriuria	2	9
Suspect carcinoma of prostata	8	-
Definitive enlargement of prostata	46	-
Urgent miction	25	24
Diabetes		
anamnestic	6	6
oral treatment	4	5
insulin treatment	1	1
Joint diseases		
back pains every week	16	28
arthralgia every week	16	27
arthralgia knee joints	5	8
Rheumatoid arthritis	3	6
Heberden s nodules	3	10
Abnormally functioning		
fingers	8	9
wrists	2	4
elbows	3	4
shoulders	4	5
hips	7	9
knees	5	10
ankles	3	4

Table I Prevalence in per cent of certain symptoms or diseases Anamnestic = life time incidence

	Males	Females
Eczema	20	18
Psoriasis	3	1
Petechia	3	6
Vascular spiders	26	4
Chronic bronchitis (WHO definition)	18	9
Pulmonary carcinoma (X-ray)	2	0
Pulmonary metastases (X-ray)	1	0
Pulmonary tuberculoses active (X-ray)	0	0
Pulmonary tuberculoses inactive (X-ray)	74	80
Myocardial infarction (Minnesota code)	6	3
Probable myocardial ischemia (Minnesota code)	13	10
Angina pectoris (according to Rose)	13	10
Atrial fibrillation	4	2
Ventricular extrasystole	6	5
Atrio-ventricular blockade	5	2
Congestive heart failure	20-25	20-25
Intermittent claudication	6	7
Hypertension		
anamnestic	23	48
treated	12	30
Cerebrovascular disease		
anamnestic	2	1
hemipareses	1	1
Headache daily	2	6
Headache at least once a week	8	15

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knees	5	10
ankles	3	4

Arcus cornae was observed in 71 per cent of males and 59 per cent of females and both arcus cornae and xanthelasmata in 7 per cent and 6 per cent respectively Cutaneous and/or tendon xanthoma were not observed in any of the patients

Fifty per cent of the males and 12 per cent of the females were smoking daily 76 per cent of the male and 64 per cent of the female smokers smoked 5 or more cigarettes per day 9 and 1 5 per cent more than 15 cigarettes per day Thirtythree per cent and 6 per cent had been smokers earlier, but had now given it up In 18 per cent of the males and in 9 per cent of the females anamnestic evidences of chronic bronchitis according to the WHO-definition were present and 20 per cent and 8 per cent respectively showed objective symptoms at the clinical examination At the roentgenological examination of the lungs pulmonary emphysema was diagnosed in 9 per cent and 1 per cent active inflammatorv disease in 2 per cent and 1 per cent respectively while changes considered to be due to earlier active but at the time of the present investigation inactive inflammatory disease were observed in 14 per cent and 12 per cent Roentgenological changes indicating earlier tuberculosis were observed in 74 per cent of the males and 80 per cent of the females Primary pulmonary malignant tumors were discovered in 2 males and pulmonary metastases in one man

Histograms for systolic and diastolic (phase 4) blood pressure for males and females are shown in Figures 1 and 2

Six per cent of the males and 3 per cent of the females had according to the Minnesota code (32) electrocardiographic evidences (Q of types I or II) of previous myocardial infarction These figures would have increased to 15 per cent and 11 per cent respectively if the occurrence of a pathological Q of type III had been

as evidence for myocardial infarction Thirteen per cent of the males and 10 per cent of the females suffered from anginal pain as defined by Rose (31) while 8 per cent and 4 per cent suffered from electrocardiographic changes of probable ischemia Four per cent and 2 per cent had atrial fibrillation 6 and 5 per cent ventricular extrasystole and 5 and 2 per cent respectively atro-ventricular blocks

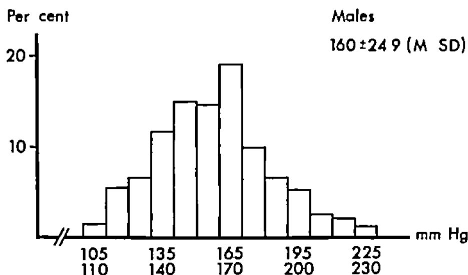
As far as symptoms of cerebro-vascular diseases were concerned 1 7 per cent of the males and 1 3 per cent of the females reported that they had been or were suffering from such diseases while 1 2 per cent and 3 0 per cent had hemiparesis at the examination

Intermittent claudication was on the other hand registered in the same frequency (6 per cent) among males and females

Fourteen per cent of the males and 29 per cent of the females had had or were suffering from symptoms of gall stone 25 per cent and 10 per cent of peptic ulcer and 4 per cent of males and 0 2 per cent of the females reported that they had hernia while such hernia was diagnosed in no less than 29 per cent of the males (0 per cent of the females) at the clinical examination

Twentyfive per cent of the males and 24 per cent of the females complained of precipitate micturition Six per cent of the males and 44 per cent of the females complained of urinary incontinence with a cough or a laugh etc and 2 per cent and 1 per cent of incontinence in the night Two and 9 per cent had significant bacteriuria Twentyfive per cent of the males had apparent dysuria 46 per cent apparent enlargement of the prostata and 8 per cent suspected and later on by biopsy verified carcinoma of the prostata

Twentyone per cent of males and 34 per cent of females



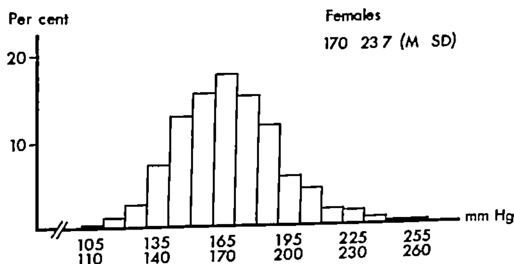
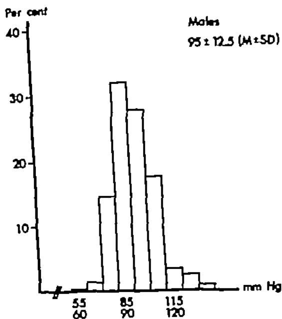


Figure 1 Systolic blood pressure



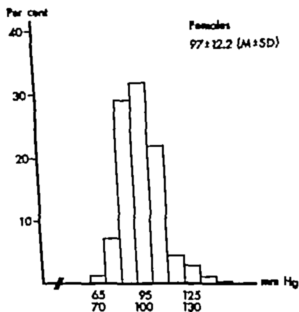


Figure 2 Diastolic (phase 4) blood pressure

reported back pains thereof 16 per cent and 28 per cent every week Sixteen per cent and 27 per cent complained of pains in peripheral joints 5 per cent and 8 per cent in the knee-joints

The 3 cases of mammary carcinoma were small and found in soft tissue X-ray examination of the breasts By the palpatory method suspect tumors were observed in 3 other women but further investigations by X-ray and biopsy showed that these abnormalities were benign Malignant tumors or highly suspected malignant tumors were observed on an average of 7 per cent of the probands

With mobility tests performed according to the method described by Gillner et al (15) 94 per cent of the males and 91 per cent of the females showed no limitation of mobility (0 points) 3 and 5 per cent showed some limitation (1 point) The highest number of scores observed was 32 points i e advanced handicaps

According to the nursing load point scale by Hultén et al (20) 94 per cent of the males and 91 per cent of the females showed 0 points 3 per cent and 5 per cent 1 point and the maximum points registered were 30 and 29 respectively

Dr Margareta Bjurö was responsible for the othological examination In conventional hearing tests 60 per cent of males and 86 per cent of females were able to hear whispering at a distance of 5 metres 29 per cent and 10 per cent ordinary conversation at this distance but 10 per cent and 3 per cent only at 1 metre distance Among the males 1 3 per cent and among the females 0 4 per cent could thus not hear ordinary conversation at a distance of 1 metre Tone and speech audiometry showed a lowering of the hearing ability of 50 decibel for speech in 8 per cent of the males and 1 per cent of the females i e on average in 5 per cent of the

As examples of retrospective longitudinal data obtained will be mentioned that almost all of the males (99 8 per cent) and half of the women (46 per cent) had had gainful employment and that the nature of their work and also the environment where they had been working was registered as carefully as possible between ages 20 40 40-60 and after 60 as well as reasons for early retirement pensions The results of global evaluation of health cognitive function and social condition in relation to previous or present occupational work will be published separately

The ophthalmological investigations performed by Dr Margareta Munkby showed e g chronic conjunctivitis in 11 per cent grey cataract with a visual acuity of < 0 5 on one eye in 4 per cent and on both eyes in 1 per cent glaucoma in 1 per cent and advanced macular degeneration in 2 per cent Reduced visual acuity with maximum correction of glasses to 50-70 per cent of normal capacity was found in 9 per cent to 20-40 per cent in 2 per cent and to 5-10 per cent in 1 per cent The examinations showed that 95 per cent were able to read the telephone book in Gothenburg and 97 per cent the standardized text on bottles and other packagings of drugs in Sweden

The psychiatric examination performed by Dr Göran Persson showed 1) Psychotic state (i e advance mental d sturbances that made it impossible for the patient to take care of himself and/or the patient no longer realized himself that he was sick); schizophrenic - paranoid psychosis 1 per cent organic lesions (senile dementia a teriosclerotic dementia traumatic or alcoholic lesion) 1 5 per cent 2) Neurotic state (i e mental disturbances of slighter grade than the above mentioned); Organic lesions (see above) 3 per cent anxiety - depression - compulsory neurosis 9 per cent

both organic and affective illness 1 8 per cent 3) Furthermore certain individuals had mental symptoms apparently due to special personality traits The psychiatric observations will be published in detail separately

The odontological study was performed by Dr Tor Österberg and will also be published in detail separately These reports will be given in odontological journals which are not usually available to others than odontologists and the results will therefore be described somewhat more detailed below Thirtytwo per cent of the 70-year-olds who underwent the odontological examination stated that their own teeth or jaws caused inconvenience and 45 per cent considered dental care necessary Almost one third of both the males and females chewed their food with difficulty Every fourth woman experienced a dryness of the mouth In this matter there was a significant sex difference ($p < 0 01$)

Almost 60 per cent of the 70-year-olds had one or more subjective sign of e g maxillary joint pains difficulties when opening the mouth and when swallowing and chewing pains all of which pointed to the fact that functional disturbances of the chewing apparatus were common

Out of the 385 examined 70-year-olds lack of own teeth on the upper and lower jaw was observed in 69 per cent and 52 per cent respectively 51 per cent were lacking teeth in the upper as well as in the lower jaws

Thirtyfour per cent of the males and 26 per cent of the females had their own teeth in both upper and lower jaw Nineteen per cent of both the males and the females had their own teeth in only one jaw Mean value of own teeth in the probands with such teeth was 13 6 More than half of the 70-year-olds had less than 15 own teeth Almost 2/3 of these teeth had had preserving

treatment The females had on average more repaired teeth than had the males Mean value for number of teeth with caries was 2 8

Eight per cent among those without teeth had been rehabilitated with upper jaw denture as early as before the age of 20 60 per cent before the age of 50 Loss of own teeth of the lower jaw came later than of the upper jaw Women lost their own teeth earlier in life than men teeth in the upper as well as the lower jaw Almost half of those with complete dentures had had the same dentures for more than 10 years and one fourth had had the same dentures for more than 20 years

As few as 14 per cent of those with complete dentures had well functioning dentures Fiftysix per cent had dentures with an unacceptable function of the upper as well as of the lower jaw and an incorrectly balanced bite Fiftyfour per cent of the females and 80 per cent of the males had an unsatisfactory hygiene of the dentures a significant difference between the sexes showed up ($p < 0\ 01$)

It is a wellknown fact that there is a relation between bad hygiene of denture bad fitting dentures and changes of the mucosa In the 70-year-old population study mucous membrane changes (denture stomatitis hyperplasia of the mucosa) of the upper jaw were found in 71 per cent of those with a complete denture A lower frequency of these changes was reported from the lower jaw Inflammatory changes were found more frequently in women than in men ($p < 0\ 01$) Among probands without teeth females had a higher frequency of ragades than males ($p < 0\ 05$)

Clinical findings at the bite physiological examination indicate that disturbances of the bite function are common in 70-year-olds Eightyfive per cent of males and females showed symptoms of disturbances of the

chewing function

In spite of the high frequency of disturbances of the bite function the movement capacity of the lower jaw was surprisingly good in the 70-year-olds The mean values of the movements the maximum ability of opening the mouth and the aside gliding were in those with teeth in the same order of magnitude as in younger individuals (1)

In order to describe the function and the degree of bite disability of the examined 70-year-olds we have used an index referring to four supporting zones of the sides of the jaws According to this index 14 per cent of those with teeth had a slight bite disability while on the other hand 51 per cent had strongly mutilated bites When the classification was made with regard to the already performed oral rehabilitation by prothetic means out of all 70-year-olds toothless as well as with teeth 9 per cent had no supporting zones of the bite and had thus a serious functional disability of the bite (37)

By analyses of serum digoxin concentrations the relevance of the interview answers concerning digitalis consumption was evaluated (23) The results indicated that the information concerning at least this drug treatment was adequate Seventyseven per cent of the females and 61 per cent of the males were on treatment with drugs and 9 per cent had 6 or more different drugs (Figure 3) (24) One woman had been prescribed 24 different drugs thereof 17 for consumption daily Every third woman was treated with sedatives and/or sleeping pills and 3 out of 10 women were undergoing treatment with diuretics The most common drugs were hypnotics-sedatives-atharactica diuretics analgetics and vasodillatantia Eight per cent of the male probands and 12 per cent of the females were aware of allergic reactions to one or more drugs

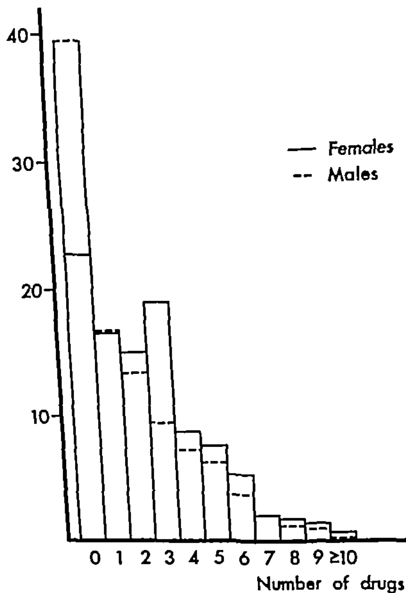


Figure 3 Percentage of probands with different numbers of drugs

Table II Laboratory analyses

		Males		Females	
		M	SD	M	SD
B-Hb	g/l	149	13 4	139	11 2
B-Erythrocytes-volume fraction (hematocrit)	%	43	3 9	41	2 8
B-Erythrocyte sedimentation rate (ESR)	mm/h	12	12 7	15	11 2
B-Glucose	mmol/l	5 66	1 512	5 54	1 630
P-Cobalamines (vitamin B_{12})	pmol/l	211	100 3	233	102 0
B-Folate	nmol/l	193	87 6	184	81 4
P-Folate	nmol/l	104	41 2	104	40 3
P-Bilirubin	µmol/l	8 5	3 57	8 5	2 55
P-alkaline phosphatases (37°C)	µkat/l	2 8	1 64	2 8	0 88
P-aspartate-amino-transferase (37°C)	µkat/l	0 34	0 182	0 34	0 216
P-alanine-amino-transferase (37°C)	µkat/l	0 25	0 160	0 22	0 226
P-sodium	mmol/l	140	2 2	140	2 0
P-potassium	mmol/l	3 8	0 37	3 7	0 40
S-protein	g/l	79	6 1	79	5 3

		Males		Females	
		M	SD	M	SD
S-creatinine	µmol/l	88	20 2	79	20 2
S urea	mmol/l	6	3 7	6	2 4
S-calcium	mmol/l	2 40	1 30	2 40	1 15
S phosphate	mmol/l	0 9	0 16	1 0	0 17
S-iron	µmol/l	18	6 9	17	5 8
S total iron-binding capacity (TIBC)	µmol/l	65	11 8	66	11 1
S urate	µmol/l	306	81 0	276	85 2
P cholesterol	mmol/l	6 1	1 19	6 7	1 34
P triglycerides	mmol/l	1 6	0 84	1 5	0 62
P-total phospholipids	mmol/l	3 37	0 529	3 73	0 564
P-lecithin	% of total phospholipids	70 1	5 48	70 2	2 07
P-lysolecithin	% of total phospholipids	5 7	1 19	5 0	0 84
P-sfingomyelin	% of total phospholipids	21 0	2 50	22 0	2 15
P-cephalin	% of total phospholipids	2 7	0 61	2 8	0 53
P-free fatty acids	mmol/l	0 17	0 085	0 21	0 089

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S-protein	g/l	79	6 1	79	5 3

Table III Frequency and causes of out-patient consultations (per cent)

Out-patient care consumption (3-year-period):

	Males	Females
> 1 time per month	1 8	2 9
1-2 times per quarter	17 5	25 3
1-3 times per quarter	30 5	39 1
< 1 time per year	31 4	22 0
never	18 8	10 7

Cause of latest out-patient call

Requested routine control	52 3	67 0
First time acute illness	32 3	16 9
Impairment of earlier known illness	12 6	8 9
Health control	2 9	7 2

The results of certain laboratory analyses (performed in in collaboration with Dr Rudolf Jagenburg) are shown in Table II Certain results of lipid analyses have been published separately (34) The results of laboratory analyses will be published separately more in detail

The psychological studies were performed by two psychologists Egil Andersson and Maria Lawenius The results of tests of vocabulari ability ability in drawing logical conclusions by the use of reasoning and figure classification and test of sensory-motor speed and coordination as well as immediate memory ability memory of figures, have been preliminary reported previously (3) Raven s coloured progressive matrices described as a test of observation and clear thinking and often used in psychogeriatrics were also used and normative data from this 70-year-old urban population was thus obtained The psychological findings will be published in detail separately A general conclusion from these tests is that the results do not indicate any marked reduction of these cognitive functions at the age of 70 with one exception namely that the sensory-motor speed was markedly lowered at that age

Table III shows the frequency of out-patient consultations and the reason to the consultation Every fourth 70-year-old proband apparently visits a doctor 4 or more times a year Women reported a higher frequency of consultations than men and also that they because of ordinated controls went more often than men On average 6 per cent of the 70-year-olds had visited a physician during the preceding year

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DISCUSSION

The observations showing such a stable population in *Gothenburg with low migration and immigration rates* were of course of extreme importance for the evaluation of the results of this study Certain studies of younger age groups of this population have previously been performed (4 19 35) and will allow certain cross-sectional comparisons between age samples as similar examination methods were used

The information obtained in conjunction with home calls was of great interest not only from a sociological point of view but also as background data for the medical gerontological as well as the clinical medical examination of this 70-year-old population sample The 2 nurses who performed the home visits found 94 per cent of the probands that accepted a home call very willing to cooperate 5 per cent indifferent and only 5 men and 2 women reluctant

About every sixth woman was living in a situation of loneliness physical and intellectual inactivity to such an extent that it could have influence upon basic physical and mental functions Fortyfour per cent of males but only 18 per cent of females go out without hesitation after dark And daylight time is short in Sweden during half of the year The fact that every sixth woman declared that one or more days could pass without contact with others is another example on social isolation The consumption of psychopharmacological drugs was significantly higher in this group than in the others Those complaining of loneliness significantly more often declared that they did not feel fit but the prevalence of diseases known to influence mobility such as chronic bronchitis and anginal ... not overrepresented among those who felt

lonely The lonely women visited physicians more often than the other women These observations seem to indicate that social isolation and physical inactivity is one explanation for the sex difference in consumption of medical care

It should also be emphasized that the detailed penetration of the social background gave in general information that was also of importance with the evaluation of the need of and possibilities of prophylactic measures in this age group The evaluation of the present material concerning possibilities for prophylactic and preventive measures in this age group will be published separately

Fortyeight per cent of the 70 year-olds said that their only hobby was reading but only about 15 per cent had enough light for reading at the location where they usually sit when reading This exemplifies again that the living conditions of the elderly in their present home situation often forces inactivity upon them Inadequate illumination must furthermore mean increased risk of accidents The result of the illumination measurements is only one example on the lack of adjustments of dwellings to the real need of the elderly

Fortytwo per cent of the probands had access to summer cottages And it was obvious that they left their well equipped and usually well functioning flat in the city and moved to less well equipped houses in the country as soon as d ylight became longer i e usually in April or May and did not return to the city until in October Apparently some of them found a more meaningful activity like gardening and often also an atmosphere with better personal contacts in the rural environment

At the present state of this longitudinal study only limited conclusions can be made concerning incidence

and prevalence of disease in this age group In many cases ageing per se causes signs very similar to symptoms of disease More adequate conclusions demand longitudinal studies A detailed study has however already been tried out in the group of probands treated with digitalis The results indicate that at least a third and possibly 50-60 per cent of these were on digitalis treatment because of signs that could have been due to normal ageing and were lacking symptoms on definable heart disease (23)

In Sweden the life expectancy at birth for males is about 73 years Women live longer (about 77 years) than men and one might therefore anticipate that they should be healthier and need less medical care than men But women consume more drugs and consult physicians more often than men As far as institutional care is concerned one reason for this sex difference is obviously that it is easier for a man to find care resources at home than a woman But as far as drug consumption and out-patient care is concerned another explanation must exist At the age of 70 urinary incontinence bacteriuria and rheumatic diseases were more common among females but respiratory diseases cardiovascular diseases cancer and liver diseases more common among males Males were thus to a greater extent suffering from life-threatening diseases which within a shorter time can be fatal The males were however apparently also suffering from a great many less serious diseases and a global judgement of the infirmity of the 70-year-olds does not indicate that the higher consumption of medical care of women is indicated by higher incidence or prevalence of diseases among 70-year-old women

The present study indicates that overdiagnosis is rather common in this age group due to the fact that the border - or the border zone - between normal ageing and disease is only a very vague presentiment

in the higher age groups The author of this report has some difficulty in accepting that 48 per cent of 70-year-old women really should suffer from hypertensive disease The distribution curves for systolic and diastolic pressure were skewed to the right but without obvious separation of a hypertensive group At the age of 70 the average systolic and diastolic blood pressures were higher in females than in males; but this does not necessarily mean that the females in the higher age groups suffer more often from a hypertensive disease indicating treatment The diagnosis of hypertension might be one example of overdiagnosis occurring to women more often than men and therefore to a certain extent explaining the higher consumption of drugs and medical service by women

The present result also showed underdiagnosis i e that previously unknown diseases often were found at this health survey During the first two stages of investigation in the out-patient department the general clinical examination and the chemical laboratory test on average one observation generally considered to indicate a disease was discovered per proband and this number was of course further increased during the other stages of the examinations On average only about 25 per cent of definable diseases observed were previously known to the probands The preliminary conclusions thus indicated that both overdiagnosis and underdiagnosis are common in this age group

The observations in the present study showed that only about 3 per cent of the 70 year-olds suffered from advanced handicaps or disease to such an extent that care within institutions was necessary The need for institutional care shows obviously an acceleration at first in higher age groups These facts have not been taken into consideration in planning of care for the elderly which is still usually calculated along a line based on the rate of incline of the

group It is of importance to clarify which age line shows the change in the average care consumers in the higher age groups of such approximative calculations

Numerous studies of the state of health as well as of social living conditions of the elderly have been performed in different parts of the world (2 4 5 6 7 8 9 10 11 12 13 14 16 17 18 19 21 22 25 26 28 30 33 35 36) To our knowledge very few epidemiological studies of elderly populations have however been performed with a basic epidemiological technique that really allows generalizations from the investigated sample to larger sections or to well definable sections of the population A general statement out of a comparison of the present observations with those of other population studies is that the social living conditions of the elderly in Europe seem to be rather similar in at least Scotland (17) Norway (14) and Sweden Observations performed in Finland (33) Norway (14) Scotland (17) and Denmark (30) also indicate that the general evaluation of the state of health and frequency of handicaps in the 70-year-old population in Gothenburg Sweden should not be too different from that observed in other studies performed in European countries with similar climatic and general living conditions

It is obvious that the elderly at least in the rural areas of the industrialized countries are rather commonly living under social conditions that from a medical point of view should be subjected to critizism The elderly often suffer from an unmet need of medical support - a need comprising both preventive actions and medical treatment It should however also be emphasized that the majority of the 70-year-olds in Gothenburg are living a very comfortable life in rather good physical and mental condition and seem to have wonderful opportunities of enjoying life

REFERENCES

1 Agerberg G & Österberg T : Maximal mandibular movements and symptoms of mandibular dysfunction in 70-year-old men and women Swed Dent J 67 no 3 1974

2 Akhtar A J : Refusal to participate in a survey of the elderly Geront clin 14 205 1972

3 Andersson E Lavenius M Persson G Rinder L Steen B & Svanborg A : Classification diagnosis and treatment of mental diseases in the elderly Age and Ageing Suppl issue:64 1975

4 Bengtsson C Blohmé G Hallberg L Hällström T Isaksson B Korsan-Bengtsen K Rybo G Tibblin E Tibblin G & Westerberg H : The study of women in Gothenburg 1968-1969 - A population study Acta med scand 193:311 1973

5 Bennett A E Garrad J & Halil T : Chronic disease and disability in the community A prevalence study Brit med J 3 762 1970

6 Berfenstam R & Hedqvist H : The vital condition and need of care of the elderly Almqvist & Wiksell AB Uppsala 1960

7 Dawber T R Kannel W B & Lyell L P : An approach to longitudinal studies in a community The Framingham study Ann N Y Acad Sci 107 539 1963

8 Dunér H Malmström G Sandberg O Sivert-Björkquist M & Möller M : Redogörelse för Hälsoundersökning av 66-åringar i Stockholms kommun Socialstyrelsen Stockholm 1973

9 Engel A Dunér H Malmström G Sjöström A & Magnu son P -H Hälsoundersökningen i Värmland 1962 1965 Social tyrelsen Civiltryck AB Stockholm 1968

10 Epste n F H An epidemiological study in a total community: The Tecumseh Project Univ Mich med Bull 26 307 1960

11 Essen-Möller E Larsson H Uddenberg C -E & White G Individual traits and morbidity in a Swedish rural population Acta psychiat neurol scand Suppl 100 1956

12 Fr sk A R Werkö L Holmgren A & Ström G Stockholm a city health survey 1954 Acta med scand 163 1 1959

13 Gardiner R : The identification of the medical and social needs of the elderly in the community a pilot survey Age and Ageing 4:181 1975

14 Gaustad V Den sosial-medisinske undersökelse av eldreomsorgen i Oslo Foreløbig oversikt Oslo 1964

15 Gillner A Hultén A Kerstell J Olsson R Steen B & Svanborg A : Intensive short-term rehabilitation of geriatric patients Scand J Rehab Med 1:133 1969

16 Gilmore A J J & Caird F I : Locating the elderly at home Age and Ageing 1 30 1972

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33 Sourander L B Ruikka I & Kasanen A A Health Survey on the Aged with a 5-Year Follow-Up Acta socio-med scand Suppl 3 1970
34 Svanborg A Bengtsson C Lindquist O Roupe S & Steen B : Plasma lipid changes in the female in aging and the menopause Results from three population studies Clin chim acta In print 1977
35 Tibblin G : High blood pressure in men aged 50 - A population study of men born in 1913 Acta med scand Suppl 470 1967
36 Van Zonnefeld R J The Health of the Aged Organization for Health Research T N O Van Gorcum Assen 1961
37 Österberg T & Landt H : Index för bettstatus för epidemiologiska studier och kliniskt bruk Tandläkartidningen 68 no 21 1976

17 Gruer R Needs of the Elderly in the Scottish Borders, Scottish Health Service Studies No 33 Scottish Home and Health Department West Calder 1975

18 Haglund G Bengtsson M A Persson A Östlund S Bovide I Gardell, I Lindberg B Lindberg M Sartz U Nyberg P Samuelsson G & Spek J -E Dalbyundersökningarna Undersökning av 67-åriga pensionärer Läkartidningen 68:4009 1971

19 Hallberg L , Högdahl A -M Nilsson, L & Rybo G : Menstrual blood loss - A population study Acta obstet gynec scand 45:2 1966

20 Hultén A Kerstell J Olsson R & Svanborg A : A method to calculate nursing load Scand J Rehab Med 1 117 1969

21 Isaacs B & Neville Y The measurement of needs in old people Scottish Health Service Studies No 34 Scottish Home and Health Department 1976

22 Kay D W K Bergmann Y Foster E M McKechnie, A A & *Roth M : Mental illness and hospital usage* in the elderly: A random sample follow up Comprehensive psychiatry 11 26 1970

23 Landahl S Lindblad B Roupe S Steen B & Svanborg A Digitalis therapy in a 70-year-old population Acta med scand In print 1977

24 Landahl S & Steen B : Läkemedelskonsumtion hos 70-åringar i Göteborg Läkartidningen 72:5158 1975

25 Malmström G Jakobsson S & Söderlund G : Försöksverksamhet med allmänna hälsoundersökningar i Gävle 1969-1970 En metodstudie Socialstyrelsen redovisar no 43 Liber distribution Stockholm 1975

26 Milne J S Maule M M & Williamson J : Method of sampling in a study of older people with a comparison of respondents and non-respondents *Brit J prev soc Med 25:37 1971*

27 National Central Bureau of Statistics: Living Conditions Report No 1 Health and Medical Care Utilization 1975 LiberTryck Stockholm 1976

28 Persson H : A male inquiry into pensioners living condition Scand gen soc Med 1 25 1973

29 Rinder L Roupe S Steen B & Svanborg A : Seventy-year-old people in Gothenburg A population study in an industrialized Swedish city I General presentation of the study Acta med scand 198:397 1975

30 Rinder Bollerup T : Prevalence of mental illness among 70-year-olds domiciled in nine Copenhagen suburbs The Glostrup Survey Acta psychiat scand 51 327 1975

31 Rose, G A The Diagnosis of Ischaemic Heart Pain and Intermittent Claudication in Field Surveys Bull Org mond *Santé/Wld Hlth Org 27:645 1962*

32 The Scandinavian Committee on ECG classification The Minnesota Code or ECG classification Adaptation to CR leads and modification of the code for ECGs recorded during and after exercise Acta med

INTAKE OF ENERGY AND NUTRIENTS AND MEAL HABITS IN 70-YEAR-OLD MALES AND FEMALES IN GOTHENBURG SWEDEN A POPULATION STUDY

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ABSTRACT

The objectives of this substudy within the population study 70-year-old people in Gothenburg Sweden were to survey the dietary habits of the probands including meal habits and intake of energy and nutrients The subsample comprised 191 males and 199 females of whom 182 males and 188 females took part in the complete dietary interview examination comprising a 24-hour recall interview and a dietary history interview The examined subsample was considered representative of the 70 year-old population in Gothenborg The dietary

well-known decreasing number of cells in the organs is not settled Favourable to the first-named hypothesis is the fact that isolated mitochondria from hearts of old rats have lower respiratory activity (18) and cytochrome content (5) If this is the case it might be due to a decreased intake of nutrients at higher ages and the subsequent adaptation of the cell or a result of a decreased cell metabolism due to ageing per se If so - this may mean a decreased need of a supply of nutrients during basal conditions in relation to body cell mass in the elderly individual compared with the need in younger age groups It may also be claimed that changes in cells and organs may lessen the ability for uptake of nutrients and that this may be compensated for by higher blood concentration of nutrients in the supplying blood In favour of the last-mentioned hypothesis might be the fact that the homeostasis of some nutrient fractions in blood is changed in such a way that the concentrations increase in higher ages e g blood glucose

There are on the other hand several facts indicating that the main reason for the lower oxygen uptake in elderly individuals is the loss of metabolizing tissue (47) and there are animal experiments which have failed to find any reduction in oxygen uptake of tissue slides homogenates or isolated mitochondria from rat heart liver or kidney (11) thus contradicting the above-mentioned studies (5 18)

There is an obvious need for more knowledge concerning the requirement of energy and nutrients in relation to body cell mass and energy output in elderly people In a survey of social and medical conditions of 70-year-old people in Gothenburg the design and procedure of which has earlier been presented (46) an attempt has been made to illustrate nutritional questions in one of the older age groups in which many individuals are still capable of an approximately similar average

history method was found to be more valid than the 24-hour recall method On an average 1 8 hot meals and 0 9 meals of type beverages and sandwich with slices of meat cheese etc were consumed daily The intakes of energy and nutrients were on average satisfactory but showed a fairly great variation Examples of intakes calculated from the dietary history interview are (M±SD males and females respectively): Energy 9 8±2 4 MJ and 8 1±2 3 MJ protein 74±18 7 g and 63± ±16 5 g calcium 1033±414 0 mg and 927±368 0 mg and potassium 79±22 2 mmol and 68±25 1 mmol respectively Examples of significant associations between social data and data of the intake of energy and nutrients are that probands with an education higher than elementary school showed a higher proportion of energy intake from protein than other probands and that males living alone showed a lower iron intake than other males A comparison between this study and cross-sectional studies on e g middle-aged women in Gothenburg showed that the energy intake and the body composition in females was of the same order of magnitude in these two groups More definite conclusions concerning possible changes by age in intake of energy and nutrients presuppose however longitudinal studies The present cross-sectional data will be used as a basis for a prospective longitudinal geriatric/gerontological study

INTRODUCTION

There is reason to believe that aged organs have a decreased metabolism To what extent this reflects a lower capacity of the single cell and/or just the

well-known decreasing number of cells in the organs is not settled Favourable to the first-named hypothesis is the fact that isolated mitochondria from hearts of old rats have lower respiratory activity (18) and cytochrome content (5) If this is the case it might be due to a decreased intake of nutrients at higher ages and the subsequent adaptation of the cell or a result of a decreased cell metabolism due to ageing per se If so - this may mean a decreased need of a supply of nutrients during basal conditions in relation to body cell mass in the elderly individual compared with the need in younger age groups It may also be claimed that changes in cells and organs may lessen the ability for uptake of nutrients and that this may be compensated for by higher blood concentration of nutrients in the supplying blood In favour of the last-mentioned hypothesis might be the fact that the homeostasis of some nutrient fractions in blood is changed in such a way that the concentrations increase in higher ages e g blood glucose

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daily physical activity as common in middle-aged people

The study comprises dietary interviews the relevance of which has been checked by analyses of urinary excretion of nitrogen The study furthermore includes other data of nutritional interest such as studies of body composition with isotope techniques and studies of the relation between oral health and nutritional data These studies will be reported in subsequent papers (29 50) whereas the present paper is the first in this series concerning nutrition of the investigated group

In this paper the relevance in this age group of the dietary interview methods used will be discussed dietary habits and intake of energy and nutrients will be presented and the intake compared to existing standards

MATERIAL

The population study 70-year-old people in Gothenburg comprised a representative systematic sample of 1148 70-year-old people in Gothenburg which was obtained from the Revenue Office Register in a way described previously (46) The propositi were numbered consecutively (1 2 3 4 5 1 2 etc) to make subsampling possible

Probands 3 and 4 who took part in the hospital part of the study (191 males and 199 females) were invited to participate in a dietary interview It was pointed out that this interview was an important complementary

part of the examination It was arranged at the hospital for a dietitian to visit the probands in their own homes some time after the hospital examination

A dietary interview was completed in 370 probands 182 males and 188 females (24-hour recall and dietary history) and 4 probands 1 male and 3 females (24-hour recall only) Non-responders from the dietary history interview were 20 probands (9 males/4 7 per cent/ and 11 females /5 5 per cent/) The reasons for this non-response were refusal and incooperability

In order to test the representativity of the dietary history interviewed probands they were compared with the other propositi in the study regarding sex marital status proportion of males registered in the Register of Temperance Board income and community rent allowances No significant differences ($p > 0\ 05$ x^2-test and Student s t-test respectively) in this register data were observed As far as height body weight waist girth triceps and subscapular skinfold B-Hemoglobin B-Glucose P-Triglycerides and S-Iron were concerned only one significant difference between this subsample and the other probands was observed on the one per cent level (Student s t-test) namely a difference in triceps skinfold thickness in the females (Table I) Our general conclusion is therefore that the subsample did not differ in physical characteristics

METHODS

As a first part of the hospital examination in the morning and in a fasting state blood samples were

Table I Comparison between mean values (M) of certain variables in probands interviewed with the dietary history method and in other probands SD: standard deviation (Student s t-test NS: p > 0 05)

	Males					Females				
	Interviewed (n=182)		Not interviewed (n=269)			Interviewed (n=188)		Not interviewed (n=334)		
	M	SD	M	SD	Sign	M	SD	M	SD	Sign
Height (cm)	174	6 8	173	6 5	NS	161	5 9	159	5 6	p < 0 05
Body weight (kg)	77 1	11 64	76 0	11 75	NS	67 5	11 94	66 5	11 15	NS
Waist girth (cm)	90 3	9 06	89 5	10 21	NS	83 0	9 12	83 3	8 91	NS
Triceps skinfold (mm)	8 5	3 63	8 8	3 82	NS	19 3	6 02	17 8	6 13	p < 0 01
Subscapular skinfold (mm)	14 6	5 10	14 2	6 02	NS	18 2	7 59	17 8	7 70	NS
B-Hemoglobin (g/l)	150	13 1	149	13 2	NS	140	10 4	138	11 5	NS
B-Glucose (mmol/l)	5 8	1 88	5 4	1 20	p < 0 05	5 6	1 77	5 5	1 53	NS
P-Triglycerides (mmol/l)	1 6	0 80	1 6	0 87	NS	1 6	0 65	1 5	0 60	NS
S-Iron (µmol/l)	18 0	6 28	18 4	7 31	NS	17 3	6 00	17 2	5 62	NS

drawn (with Vacutainer® technique) from an antecubital vein without atasis and with the proband in the sitting position Blood was collected in one 5 ml EDTA glass tube used for determination of 1 a B-Hemoglobin in 10 ml heparin tubes which were immediately centrifuged and in 10 ml glass tubes where the blood was left to clot for three hours at room temperature and then centrifuged Plasma and serum which were not analysed fresh were stored at -18° C in sealed glass ampoules Capillary blood was collected from the finger tip for estimation of blood glucose level

B-Hemoglobin was determined with the methemoglobin-cyanide method and B Glucose with the o-toluidin method described by Härtel et al (32) S-Iron and S-Total iron binding capacity (TIBC) were determined with autoanalyzer technique using conventional methods P-Cyano-cobalamines (Vitamin B_{12}) were determined with the microbiological method of Hutner et al (31) using Euglena Gracilis (Z-strain) P-Folate was assayed with Lactobacillus casei according to a modification of the technique described by Hanson (28) P-Potassium was determined using conventional flame photometry Total P-Protein was determined with a standard biuret method P-Cholesterol was determined with the gas-liquid chromatographic method described by Blomhoff (13) and modified by Lillienberg and Svanborg (35) and S-Triglycerides according to Carlson and Wadström (17) Skinfold measurements were performed with a Harpenden caliper (21) with a pressure of 10 g/mm^2 applied at a contact surface of 20 mm^2 The skinfold was measured at the back of the right upper arm midway between acromion and elbow with the arm hanging relaxed and with the fold running parallel to the length of the arm - subject standing - (triceps skinfold) and just below the angle of the right scapula with the fold parallel to the natural cleavage line of the skin -

subject standing - (subscapular skinfold) Waist girth was measured horizontally half-way between the lowest floating ribs and iliac crests - subject standing

The dietary interviews were performed in the probands own homes on an average of 23 days after the hospital examination The interview was carried out on 242 probands (65 per cent) within two weeks and on 276 probands (74 per cent) within four weeks after the hospital examination The longest interval was 191 days for one proband due to the fact that this proband was not at home at the time originally agreed upon and thereafter was difficult to get in touch with

The same dietitian (Inga-Lill Landin) interviewed all the probands The interview was performed according to the 24-hour recall method the principle of which was originally introduced by Wiehl (56) and the dietary history method originally described by Burke (15)

As stipulated in the 2 4 - h o u r r e c a l l method the probands were interviewed about their food consumption during the last 24 hours They were asked about the number and distribution of meals throughout these 24 hours and the composition of the meals The classification of the meals used is described in Table II

The choice of food items is described in terms of 7 food groups in accordance with the usage of the Swedish National Food Administration (former National Institute of Public Health) - see (57)

- green vegetables
- fruit/berries
- potatoes/other starches
- milk products
- meat/fish/eggs
- bread/other flour products
- fats/oils for cooking and spreading

Table II Different types of meals

M	Hot meals: Cooked and fried dishes
S_1	Beverages: Lemonade juice coffee tea beer wine clear soup Sandwiches with slices of meat cheese etc
S_2	Beverages: see S_1 Biscuits cakes buns pastry etc plain bread and butter
S_3	Milk: all kinds of milk cocoa cream fermented milk Sandwiches with slices of meat cheese etc
S_4	Milk see S_3 Biscuits cakes buns pastry etc Cornflakes Plain sandwiches
S_5	Cannot be classified as above e g beverages only (a plain cup of coffee/tea was however not noted) Sweetmeat raisins desserts only and fruit only

Furthermore data on consumption of alcoholic beverages sugar and sweet meat is given

The probands were asked if their 24-hour recall was given regarding a representative day The probands also answered questions of socio-dietary interest e g facilities for cooking and storage of food

The d i e t a r y h i s t o r y method is aimed to illustrate the ordinary diet of the probands - as was pointed out to them A questionnaire especially adopted to this material was used For each food item the probands were asked about the frequency of consumption of that particular item and also about the size of the portion A cross-check of the answers was made throughout the interview One example of such cross-checking - after a detailed penetration of the number of sandwiches with different kinds of bread with or without slices of meat cheese etc - was to check that the number of sandwiches so obtained was the same as the number given earlier in the interview as an answer to the general question: How many sandwiches a day do

you usually eat? Another example was checking that the daily number of claimed lumps of sugar in cups of coffee corresponded to the earlier claimed daily number of cups of coffee To facilitate the estimation of the size of portions models of food articles were shown to the probands in some cases

The intake of energy and nutrients was then calculated using a computer system worked out at the Department of Clinical Nutrition University of Gothenburg (10) The system is mainly based on data published by Abramson (4)

Contrary to the 24-hour recall method the data from the dietary history method does not include information about the consumption of wine and liquor (Beer consumption is however included) The consumption of wine and liquor was asked for separately in a more general way at the end of the other interviews in order to minimize the risk of poor cooperation The results of the dietary history interviews below do not include this data which is reported separately However in about 3 per cent of males (because of wine consumption) and in about 10 per cent of males (because of liquor consumption) an underestimation of the energy intake must be suspected because of this Such an underestimation is on average neglectable in females

In order to investigate possible differences throughout the year regarding the calculated intake of energy and nutrients an intermonth analysis of variance and a comparison between the period April to September and the period October to March respectively were performed Since the primary interest in those analyses was focused towards differences between the periods rather than the absolute levels of intake and since the dietary history method (which aims to describe the ordinary diet of the proband) can be expected not to reveal to the same extent such possible seasonal

differences the results of the 24-hour recall method were used in these analyses

In order to study the association of some social and medical variables with data of intake of energy and nutrients a series of hypotheses was tested Thus contrast groups were studied regarding 14 dietary variables (Table III) The contrast groups were either dicotomic (e g living alone - not living alone) or extreme groups (e g upper quartile - lower quartile of a continuous laboratory variable) Thus 27 pairs of contrast groups were studied with respect to intake of energy and nutrients i e altogether 378 hypotheses The differences between the contrast groups were tested with Student s t-test or - in the case of small groups - with the Mann-Whitney U-test In these studies of possible associations of certain social and medical variables with nutrition data only test results significant on the one per cent level are reported When such significance was observed in only one sex significant results on the 5 per cent level are also given for the other sex

Table III Dietary intake variables (dietary history method) tested in the hypotheses (see text)

Energy
Protein
Proportion of energy from protein
Fat
Proportion of energy from fat
Carbohydrates
Proportion of energy from carbohydrates
Calcium
Iron
Potassium
Vitamin A
Thiamin
Riboflavin
Ascorbic acid

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Table IV Intake of energy and nutrients calculated with 24-hour recall method (24-R) and with dietary history method (DH) in those probands (182 males and 188 females) who participated in both interviews M mean value SD standard deviation

	Males					Females				
	24-R		DH		Average 24-R value in per cent of average DH value	24-R		DH		Average 24-R value in per cent of average DH value
	M	SD	M	SD		M	SD	M	SD	
Energy (kcal)	2121	590 0	2344	574 3	90 5	1672	548 9	1928	545 3	86 7
(MJ)	8 9	2 5	9 8	2 4		7 0	2 3	8 1	2 3	
Protein (g)	67	20 3	74	18 7	90 5	56	18 5	63	16 5	88 9
Fat (g)	88	30 3	96	32 3	91 7	69	27 9	80	30 1	86 3
Carbohydrates (g)	250	79 8	279	73 4	89 6	198	68 8	227	73 8	87 2
Calcium (mg)	789	394 1	1033	414 0	76 4	718	343 8	927	368 0	77 5
Iron (mg)	14 1	4 82	16 5	4 17	85 5	11 7	5 00	14 0	4 37	83 6
Potassium (mmol)	65	20 6	79	2 2	82 3	56	17 2	68	25 1	82 4
Vitamin A (µg retinol)	956	684 2	1505	801 5	63 5	899	1034	1357	684 2	66 2
Thiamin (mg)	1 3	0 53	1 4	0 35	92 9	1 0	0 40	1 2	0 43	83 3
Riboflavin (mg)	1 4	0 63	1 8	0 61	77 8	1 3	0 78	1 6	0 54	81 3
Ascorbic acid (mg)	73	47 2	82	41 7	89 0	80	52 5	87	53 7	92 0

On the visit by the dietitian to the probands homes oral and written information was given regarding the sampling of a 24-hour urinary volume from 7 a m the following morning The urine was then collected by the dietitian on a second visit and then frozen A report was written out with data of the dietitian s judgement of the reliability of the urinary sampling On the basis of this report urine volumes were judged as adequate or not Urinary nitrogen was analyzed using the Technicon Autoanalyzer Method N-3b The average non-urinary loss of nitrogen was estimated to be 2 0 g of nitrogen per day (10)

In the statistical analyses x^2-test Student s t-test the Mann-Whitney U-test and analyses of variance were used The method used is referred to in the text In situations when many variables were tested and the mass significance problem thus was actual results were considered significant only at the one per cent level in this report

RESULTS

Dietary history versus 24-hour recall

A comparison of the results of the two methods used for the calculation of the intake of energy and nutrients was made in those probands in whom both methods were used (Table IV) The average 24-hour recall values were constantly lower than the dietary history values The average calculated intake of energy protein fat and carbohydrates was with the 24-hour recall method about 90 per cent of the dietary history values but

energy and nutrients and the description of the number and kind of meals throughout the day where the 24-hour recall results were used

Number of meals

The probands had - from the dietary history - on average 4 5±0 99 (males) and 4 3±0 79 (females) meals a day (M±SD) with a range of 1-7 (males) and 3-6 (females) The daily number of hot meals was in no male and 1 female no hot meal in 48 males and 51 females one hot meal in 12[illegible] males and 123 females two hot meals and in 9 males and 13 females three hot meals

The results below regarding the numbers and kinds of meals throughout the day are taken from the 24-hour recall interview with those probands who claimed their 24-hour recall to refer to a representative 24-hour period (77 per cent of males and 75 per cent of females) The number of meals are given in Table V which shows that on average 2 7 meals of the types hot meals (H) and beverages and sandwiches with slices of meat cheese etc (S_1) were consumed daily

Table V Average daily number (M) of different types of meals (see Table II) per proband SD: standard deviation

Type of meals	Males (n=141)		Females (n=142)	
	M	SD	M	SD
H	1 8	0 56	1 8	0 72
S_1	0 9	0 79	0 9	0 81
S_2	1 2	0 89	1 1	0 84
S_3	0 3	0 50	0 3	0 43
S_4	0 1	0 30	0 1	0 29
S_5	0 1	0 28	0 1	0 39

even greater differences were observed in the calculation of intake of certain nutrients As far as intake of vitamin A was concerned the 24-hour recall method only revealed about 65 per cent of the dietary history values The correlation coefficients between data obtained from the two methods varied between r=0 66 (energy females) and r=0 26 (fat males) All coefficients differed significantly (p < 0 001) from 0

The validity of the two interview methods was tested by a comparison of the intake of protein calculated from the interviews and from the results of analyses of nitrogen in 24-hour urinary samples in those 349 probands (172 males and 177 females) in whom the urinary sampling was considered adequate The 24-hour urinary excretion of nitrogen was 10 2±3 55 in males and 8 6±2 31 g in females (M±SD)

When the intake of protein was calculated from the sum of the average urinary nitrogen excretion values and the estimated non-urinary losses an estimated average total nitrogen loss of 12 2 g (males) and 10 6 g (females) was obtained The corresponding protein figures (nitrogen figure multiplied by 6 25) were 76 g (males) and 66 g (females) These values are very similar to and not significantly (p > 0 05 Student s t-test) different from those obtained by using the dietary history method (74 g and 63 g respectively) but significantly higher (p < 0 001 Student s t-test) than the interview values obtained using the 24-hour recall method (67 g and 56 g respectively)

These studies of the validity of the interview methods strongly support the conclusion that the dietary history method had given the most valid results In this report only results of the dietary history method are reported below with two exceptions namely the analysis of possible seasonal variation in intake of

energy and nutrients and the description of the number and kind of meals throughout the day where the 24-hour recall results were used

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The probands had - from the dietary history - on average 4 5±0 99 (males) and 4 3±0 79 (females) meals a day (M±SD) with a range of 1-7 (males) and 3-6 (females) The daily number of hot meals was in no male and 1 female no hot meal in 48 males and 51 females one hot meal in 125 males and 123 females two hot meals and in 9 males and 13 females three hot meals

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Type of meals	Males (n=141) M	SD	Females (n=14.) M	SD
H	1 8	0 56	1 8	0 72
S_1	0 9	0 79	0 9	0 81
S_2	1 2	0 89	1 1	0 84
S_3	0 3	0 50	0 3	0 43
S_4	0 1	0 30	0 1	0 29
S_5	0 1	0 28	0 1	0 39

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Choice of food groups in the different types of meals

Table VI illustrates the proportion of the three most common kinds of meals in which different food groups were included

About one third of the hot meals contained green vegetables and about one fourth fruit/berries There was a slight female dominance for both of these food groups Potatoes/other starches were included in only half of the hot meals The majority of hot meals included milk products and the same was true for meat/fish/eggs and bread/other flour products A little more than half of the hot meals included fats for cooking and/or spreading Thirtyseven per cent of hot meals in males and 39 per cent in females included more than four food groups (Table VII)

Table VII Percentage of hot meals containing different number of food groups

Number of food groups	Males	Females
1	1	1
2	7	11
3	19	16
4	37	34
5	25	26
6	10	10
7	2	3

Seventyfive per cent (males) and 84 per cent (females) of the S_1 type of meals included milk products slightly less than half of these meals included meat/fish/eggs

Table VI Percentage of hot meals (M) meals including beverages and sandwiches with slices of meat cheese etc (S_1) and meals including beverages and buns etc or beverages and sandwiches without slices of meat cheese etc (S_2) which included different food groups

	M		S_1		S_2	
	Males	Females	Males	Females	Males	Females
Green vegetables	31	39	7	8	1	0
Fruit/berries	20	27	7	9	3	3
Potatoes/other starches	52	56	2	2	0	1
Milk products	70	80	75	84	32	39
Meat/fish/eggs	89	84	48	44	0	0
Bread/other flour products	82	82	100	100	100	100
Fats	62	52	96	98	27	24

Table VIII Average daily number (M) of different types of meals (see Table II) per proband in those interviewed probands (F) belonging to upper quartile of the /difference between body weight and ideal body weight (36)/ divided by body weight and other interviewed probands (NF) SD standard deviation

Type of meals	Males				Females			
	F (n=35)		NF (n=106)		F (n=33)		NF (n=109)	
	M	SD	M	SD	M	SD	M	SD
M	1 8	0 51	1 8	0 58	1 7	0 64	1 8	0 70
S_1	0 8	0 68	0 9	0 82	0 8	0 71	0 9	0 85
S_2	1 2	0 79	1 2	0 91	1 1	0 68	1 1	0 88
S_3	0 1	0 36	0 3	0 48	0 2	0 39	0 3	0 44
S_4	0 1	0 24	0 1	0 30	0 1	0 24	0 1	0 31
S_5	0 1	0 28	0 1	0 28	0 2	0 39	0 1	0 40

and only a few per cent potatoes/other starches These meals contained green vegetables in less than ten per cent and the same applied fruit/berries (Table VI)

Daily meal pattern

The distribution throughout the day of the 3 most common types of meals (M, S_1 and S_2) is given in Figures 1-2 Hot meals were more often consumed at dinner time than at lunch time Meals of types S_1 and S_2 were distributed more evenly throughout the day

In order to elucidate if obese probands had a different daily number of meals and/or different distribution of meals throughout the day the meal habits of probands belonging to the upper quartile of /the difference between body weight and ideal body weight (36)/ divided by body weight in the total material were compared with the meal habits of the rest of the material A rather good correlation (r=0 71 males and r=0 91 females) has been found in a subsample of this material between the above mentioned difference and body fat calculated from the body composition studies (50) No significant ($p > 0\ 05$ Student s t-test) differences between the obese and the other probands were found regarding the number of the three quite dominating types of meals namely hot meals and meals type S_1 and S_2 A low-grade ($p < 0\ 05$ Student s t-test) significant difference was however found regarding the number of meals type S_3 where obese males showed fewer such meals The absolute number of these meals was however very small and our general conclusion is therefore that these obese probands generally did not differ from the rest of the material regarding number of meals (Table VIII)

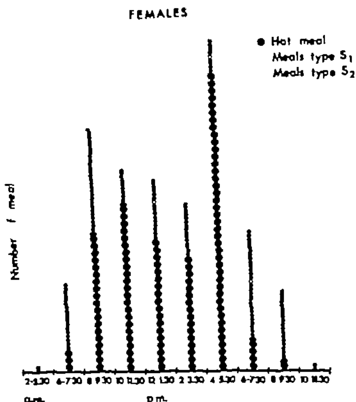


Figure 2 Distribution of hot meals meals including beverages and sandwiches with slices of meat cheese etc (S_1) and meals including beverages and buns etc or beverages and sandwiches without slices of meat cheese etc (S_2) throughout the day (females) Each full symbol represents two females

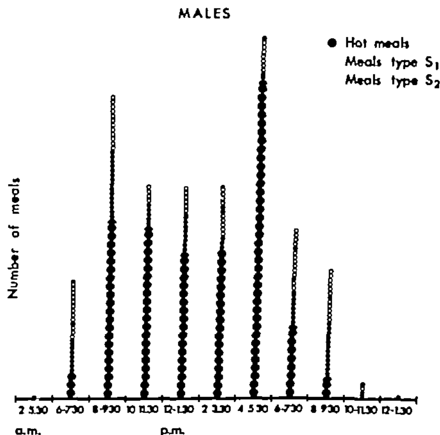


Figure 1 Distribution of hot meals meals including beverages and sandwiches with slices of meat cheese etc (S_1) and meals including beverages and buns etc <u>or</u> beverages and sandwiches without slices of meat cheese etc (S_2) throughout the day (males) Each full symbol represents two males

Table IX Storage facilities for food (per cent)

	Males	Females
None	1	1
Larder only	4	3
Refrigerator only	8	10
Larder + refrigerator	56	67
Larder + freezer	1	1
Refrigerator + freezer	4	5
Larder + refrigerator + freezer	27	14

Table X Proportion of answers to the question: Who does usually the cooking? (per cent)

	Males	Females
Proband	21	98
Spouse	72	0
Relative	3	1
Friend	1	1
Domestic help home care for the aged	2	1
Eating out	2	0

Alcoholic beverages

In males daily consumption of beer/lager was reported in 31 per cent of wine in 3 per cent and of liquor in 10 per cent (Table XI) It should be noted that data about wine and liquor consumption is not included in the results from the dietary history interview Energy data does however include energy derived from beer/ lager which however contributes to energy intake in

Regarding the distribution of the different kinds of meals throughout the day there were no obvious differences between the obese group and the other probands regarding hot meals and meals of type S_1 However in females significantly ($p < 0\ 01$ x^2-test) more meals of type S_2 were eaten before noon than after noon in the obese group compared to the other probands This difference was not observed in males Furthermore in 48 per cent of the obese females a meal of type S_2 was their first meal in the morning compared with 26 per cent in other females ($p < 0\ 05$ x^2-test) The proportion of hot meals was the same in the two groups of females When the meals of types S_1 and S_2 that *broke the fast were analysed separately 30 per cent* of the meals were of type S_1 and 70 per cent of type S_2 in the obese female group compared to 61 per cent and 39 per cent respectively in the other females ($p < 0\ 05$ x^2-test)

Kitchen facilities and cooking

Practically all probands (99 per cent) had the possibility of cooking regarding access to a kitchen (males 97 per cent females 94 per cent) or kitchenette About as many probands had an electric cooker (55 per cent) as had a gas-cooker (43 per cent) and only one proband had a wood stove as her only cooking facility Only a few probands (4-5 per cent) had no refrigerator 32 per cent of males and 20 per cent of females had a freezer (Table IX) Frozen dishes were bought sometimes or often in less than a fifth of the probands About 20 per cent of the male probands did their own cooking In fact these were with few exceptions the male probands living alone (*Table X*)

Table XII Intake of energy and nutrients calculated with the dietary history method M: mean value SD standard deviation 1st: 1st decentile m median value 9th: 9th decentile

	Males					Females				
	M	SD	1st	m	9th	M	SD	1st	m	9th
Energy (kcal)	2344+	574 3	1728	2292	2951	1928+	545 3	1262	1888	2578
(MJ)	9 8	2 4	7 3	9 6	12 4	8 1	2 3	5 3	7 9	10 8
Protein (g)	74	18 7	51	72	97	63	16 5	45	61	85
Fat (g)	96	32 3	63	91	130	80	30 1	47	77	117
Carbohydrates (g)	279	73 4	201	274	366	227	73 8	141	221	315
Calcium (mg)	1033	414 0	514	1021	1632	927	368 0	514	885	1384
Iron (mg)	16 5	4 17	11 7	16 0	21 4	14 0	4 37	9 0	13 3	19 6
Potassium (mmol)	79	22 2	52	78	109	68	25 1	46	65	97
Vitamin A (μg retinol)	1505	801 5	678	1281	2881	1357	684 2	555	1242	2287
Thiamin (mg)	1 4	0 35	1 0	1 4	1 9	1 2	0 43	0 8	1 2	1 7
Riboflavin (mg)	1 8	0 61	1 0	1 8	2 6	1 6	0 54	1 0	1 5	2 3
Ascorbic acid (mg)	82	41 7	38	76	129	87	53 7	34	74	162

+ Further daily intake of energy from wine and liquor was reported by about 10 per cent of males and 1-2 per cent of females (Table XI)

Table XI Proportion of answers to the questions Do you drink beer and lager wine and liquor? respectively (per cent)

	Beer/lager		Wine		Liquor	
	Males	Females	Males	Females	Males	Females
Never or a few times a year	40	69	85	87	62	91
Every week but not every day	29	24	12	12	28	9
Every day ≤ 1/2 bottle	28	7	3	1	8	1
Every day > 1/2 bottle	3	0	0	0	2	0

The intake of energy and nutrients - with the exception of Vitamin A and ascorbic acid - was generally higher in probands with 6-7 meals a day than in probands with 1-3 meals a day Such a difference was not observed when probands with 3 cooked meals a day were compared with probands with 0-1 cooked meals a day - except for energy and iron intake in females (Table XIV)

The intermonth analysis of variance revealed no significant differences on the one per cent level When the winter half of the year (October-March) was compared with the summer half (April-September) a significant difference was obtained in males regarding the intake of fat ($p < 0\ 01$) with a higher average value during the winter half of the year It should be mentioned that possible significant differences ($p < 0\ 05$) were observed regarding intake of energy and protein with higher average values also during the winter

In the studies of possible associations of certain social and medical variables with nutrition data the following significant results were obtained (Table XIV) Among the social hypotheses tested probands with an education higher than elementary school showed a greater proportion of energy intake from protein than other probands and the protein proportion of energy and potassium intake was correlated to income in males Males living alone showed a lower iron intake than other males

As far as possible correlations between medical history data and dietary intake were concerned differences were only observed in the diabetics (Table XIV) Females with diabetes showed a higher proportion of energy intake from protein than other females and males with diabetes reported a lower intake of carbohydrate and a lower proportion of energy intake from carbohydrates than other males Probands who claimed they felt healthy did not differ from other probands

males in an average order of magnitude of only 2 per cent

Sugar and sweetmeat

The average energy intake from lumps of sugar and powdered sugar was 94 kcal/0 4 MJ in males and 53 kcal/0 2 MJ in females The average energy intake from candies chocolate and bonbons was 30 kcal/0 1 MJ in males and females The average proportion of energy from sugar and sweetmeat thus amounted to 5 per cent for males and 4 per cent for females

Intake of energy and nutrients

Table XII gives the calculated intake of energy and nutrients obtained from the dietary history interview method and Table XIII gives the proportion of energy intake from protein fat and carbohydrates respectively An evaluation of the intakes obtained is made in the discussion

Table XIII Average proportion of energy intake (M) from protein fat and carbohydrates respectively (per cent) SD: standard deviation

	Males		Females	
	M	SD	M	SD
Protein	13 0		13 7	
Fat	37 9		38 4	
Carbohydrates	48 9		48 3	

(Table XIV cont)	Contrast groups		Significant results	
	I	II	Males	Females
	Peptic ulcer	Not peptic ulcer		
	Digitalis treatment	Not digitalis treatment		
Examination	Upper quartile of triceps skinfold	Lower quartile of triceps skinfold		Fat[b] (xx)
	subscapular skinfold	subscapular skinfold		
	waist girth	waist girth		
	height	height	Protein[a] (xx)	
	/body weight minus ideal body weight (36)/divided by body weight	/body weight minus ideal body weight (36)/divided by body weight	Protein proportion of energy[a] (xx)	Energy[b] (xx) protein proportion of energy[a] (x)
Laboratory analyses	Upper quartile of B-Hemoglobin	Lower quartile of B Hemoglobin		
	B-Glucose	B-Glucose		
	S-Iron	S Iron		
	S-TIBC	S-TIBC		

Table XIV Result of tests of hypotheses (see text) Significant results are given on the 0 1 per cent level (xxx) and the 1 per cent level (xx) - x^2-test Student s t-test - and in the opposite sex also on the 5 per cent level a: contrast group I higher value b: contrast group II higher value

	Contrast groups		Significant results	
	I	II	Males	Females
Social interview	Living alone	Not living alone	Iron[b] (xx)	
	Upper quartile of income	Lower quartile of income	Protein proportion of energy[a], potassium[a] (xx)	
	Registered at Temperance Board	Not registered at Temperance Board		
	Higher education than elementary school	Elementary school	Protein proportion of energy[a] (xx)	Protein proportion of energy[a] (xxx)
History	Feels healthy	Does not feel healthy		
	Diabetes	Not diabetes	Carbohydrate proportion of energy[b] (xxx) carbohydrates[b] (xx)	Protein proportion of energy[a] (xxx)
	Gallstone	Not gallstone		

regarding dietary intake This was also the case in patients treated with digitalis

Tall male probands had a higher intake of protein than short ones (Table XIV) Female probands with a high ratio /body weight - ideal body weight (36)/ to body weight reported a lower intake of energy than female probands with a low such ratio and all such probands reported a higher proportion of energy intake from protein than probands with a low such ratio Female probands with a high triceps skinfold value showed a lower intake of fat than females with a low triceps skinfold value

Generally speaking dietary intake did not differ in the high and low quartile groups regarding laboratory analyses (Table XIV) However female probands with a high B-Folate value showed a higher intake of vitamin A ascorbic acid potassium thiamin and riboflavin than females with a low B-Folate value Probands with a high P-Cyano-cobalamines (Vitamin B_{12}) value had a higher proportion of energy intake from protein than probands with a low P-Cyano-cobalamines value Male probands with a high P-Cholesterol value showed a higher intake of potassium than males with a low P-Cholesterol value

A comparison of dietary intake of protein calcium iron and potassium and their concentrations in blood showed no significant correlations

le XIV cont)

	Contrast groups		Significant results	
	I	II	Males	Females
	P-Cyano-cobalamines (Vitamin B_{12})	P-Cyano-cobalamines (Vitamin B_{12})	Protein proportion of energy[a] (xx)	Protein proportion of energy[a] (xx)
	B-Folate	B-Folate	Ascorbic acid[a] (x)	Vitamin A[a] ascorbic acid[a] (xxx) potassium[a] thiamin[a] riboflavin[a] (xx)
	P-Potassium	P-Potassium		
	P-Protein	P-Protein		
	P-Cholesterol	P-Cholesterol	Potassium[a] (xx)	
	S-Triglycerides	S-Triglycerides		
.etary interview	Upper quartile of food cost per month	Lower quartile of food cost per month		
	1-3 meals a day	6-7 meals a day	Energy[b] carbohydrates[b] (xxx) fat[b] iron[b] thiamin[b] potassium[b] (xx) protein[b] calcium[b] riboflavin[b] (x)	Energy[b] protein[b] carbohydrates[b] calcium[b] iron[b] thiamin[b] riboflavin[b] (xxx) fat[b] potassium[b] (xx)
	0-1 hot meal a day	3 hot meals a day		Energy[b] iron[b] (xx)

studies in younger persons possible special dietary habits during Sundays will not have any great influence on the results (10)

Even though there was rather good agreement between the protein intake data obtained with the dietary history method and the intake calculated from urinary nitrogen analyses in the total material it might be suspected that certain groups of individuals e g those with diabetes and/or obesity might report dietary habits closer to prescribed diet than their actual food intake Thus probands belonging to the upper quartile of /body weight - ideal body weight (36)/ divided by body weight apparently underestimated their dietary intake Their average protein intake calculated with the dietary history method (74 g and 51 g for males and females respectively) was apparently lower ($p < 0.05$ Student s t-test) than the corresponding figure obtained from calculation from urinary analyses (85 g and 66 g respectively) Probands belonging to the lower quartile of this ratio did not show such a discrepancy In 12 male patients with earlier known and treated diabetes the average reported protein intake according to the dietary history method was apparently lower (72 g) than the protein intake calculated from urinary nitrogen analyses (85 g $p < 0.05$ Student s t-test) It thus seems that the male diabetics underestimated their dietary intake In 13 female diabetics the corresponding figures were 66 and 72 g respectively ($p > 0.05$ Student s t-test) but the diabetic females reported a higher ($p < 0.001$ Student s t test) proportion of energy intake coming from protein than other female probands

There exist numerous reports with recommendations regarding intake of certain nutrients and reference values for energy consumption In the comparison between the present results and this data our discussion will be mainly restricted to two earlier

The general design of this population study the evaluation of basic epidemiological methods and intra- and interobserver variation studies have been reported earlier (46) That report included an intraobserver variation study of the calculation of the intake of energy and nutrients performed by the dietitian which showed no significant differences (p > 0 05 Student's t-test) between the results of calculations of dietary history values from 40 consecutive probands of intake of energy and nutrients performed by the same dietitian on two different occasions The available data indicates that the sampling techniques and methods used for collection registration and processing of data were adequate

As motivated earlier the data obtained from the 24-hour recall method was only used in the analyses of possible seasonal variation in intake of energy and nutrients and in the description of number and kinds of meals The way the 24-hour recall method was used in the present study can be criticized as no interviews covered the dietary habits on Fridays and Saturdays *It is of course possible that the probands ate more* just on Fridays and Saturdays and thus compensated for a lower food intake during the rest of the week Our results of the comparison of the urinary excretion of nitrogen and the protein intake showed that the correspondance between the dietary history method and the calculations from urinary analyses was good No urinary sampling was however performed on Sundays and Mondays The possibility that the 70-year-olds consumed more or less energy during Sundays than during the rest of the week should of course be taken into consideration However this was not the case in the present material and as far as can be judged from

males very similar average figures regarding calculated energy expenditure (2329 kcal/9 8 MJ) and energy intake calculated with the 2-days record method (2399 kcal/ 10 1 MJ) The average calculated energy expenditure in females in that study (1943 kcal/8 2 MJ) was close to the figures in this study The calculated energy intake in the study by Lonergan et al (37) was however lower (1733 kcal/7 3 MJ) The variation of intake of energy in the present study was fairly great Thus the upper decentile value exceeded RDA 1974 by more than 500 kcal/2 1 MJ (males) and by more than 700 kcal/ 2 9 MJ (females) This need not necessarily be interpreted as overeating but as a result of more pronounced physical activity compared with the average 70-year-old person The lower decentile value was almost 700 kcal/2 9 MJ (males) and more than 500 kcal/ 2 1 MJ (females) below the RDA 1974

Protein

As far as the need of dietary protein is concerned Veiledning considers 0 9 g protein per kg body weight a high intake 0 8 g per kg body weight an acceptable intake and 0 7 g per kg body weight a low/minimum intake RDA 1974 recommend 0 8 g per kg body weight According to the figure of theoretical safe level of protein by FAO/WHO (23) the level of dietary protein is lower 0 57 g protein per kg body weight in males and 0 52 g in women but this statement is valid for proteins like egg and milk proteins The average protein intake per kg body weight in this study was 0 97 g (males) and 0 95 g (females) The corresponding median values were 0 95 g (males) and 0 92 g (females) Thus on an average the intake of protein was high in the upper decentile groups very high Female probands in the lower decentile group had however an intake below the low/minimum value of Veiledning In fact

reports i e Veiledning til vurdering og planlegging av kosthold by Eeg-Larsen et al 1971 (22) referred to in the text as Veiledning and Recommended Dietary Allowances 8th Edition by the Food and Nutrition Board 1974 (24) referred to in the text as RDA 1974 Three steps are given in Veiledning (high acceptable and low/minimum) for the intake of nutrients in order to make an evaluation of the diet of adults possible RDA 1974 is "designed for the maintenance of good nutrition of practically all healthy people in the U S A In this context the RDA 1974 values are taken from the data in the group of persons 51 years of age and older

In Sweden the National Food Administration gives recommendations of nutrients per 1000 kcal/4 2 MJ However these recommendations are intended to be used in heterogenous groups of individuals which is the reason why we have chosen to compare the intakes with the data of Veiledning and RDA 1974 in this presentation

Energy

RDA 1974 gives an energy value for males 51 years and over of 2400 kcal/10 1 MJ and for females 1800 kcal/7 6 MJ Veiledning gives similar values for individuals 55-75 years and over (2400 kcal/10 1 MJ and 1700 kcal/7 1 MJ for males and females respectively) These figures thus refer to persons both younger and older than 70-year-olds Furthermore the reference persons in RDA 1974 and Veiledning have a lower body weight than the probands of the present material Our figures are close to those of RDA 1974 and Veiledning regarding males Furthermore Lonergan et al (37) studied the energy expenditure of elderly people according to principles of Durnin and Passmore (20) and found in

Iron

Both Veiledning and RDA 1974 give a recommended iron value of 10 mg On an average the intake of iron was thus high The lower decentile value was in males above 10 mg but fell in females just below It has been shown, e g (12) that the composition of the food markedly influences the utilisation of food iron As far as can be judged from the dietary interviews none of the 70-year-olds were vegetarians or otherwise kept to a diet that would significantly restrict the utilization of the food iron

Potassium

Veiledning does not mention daily potassium intakes in relation to evaluation of diets RDA 1974 just states that healthy adults need about 2 5 g per day of potassium (about 65 mmol) Judge and Cowan (34) claim that the minimal satisfactory dietary intake of potassium per day is 60 mmol The average potassium intake in the present study 79 mmol in males and 68 mmol in females thus seems acceptable However probands in the lower quartile regarding potassium intake might be judged to have a low intake especially in females

Vitamin A

Veiledning s 3-step-scale regarding vitamin A gives values of 750-600-400 µg retinol The RDA 1974 value is 5000 IU (males) and 4000 IU (females) which for American dietary habits means 870 µg and 700 µg retinol for males and females respectively (22) The average retinol intake in the present study was thus very high The lower decentile value was however lower

16 males (8 8 per cent) and 23 females (12 2 per cent) had a protein intake of less than 0 7 g per kg body weight The quality of the protein in the food was apparently good as the main part was derived from milk products meat fish and egg

Fat

The average proportion of energy from fat was 38 per cent in both sexes This is a higher value than the often recommended 25-35 per cent (e g Veiledning) However it is not exceptionally high but in the same order of magnitude as in the Food Balance Sheet in Sweden at the time of the investigation (54) 0 6 per cent of male probands and 1 6 per cent of females showed a proportion of energy from fat of less than 25 per cent and 70 0 per cent (males) and 70 2 per cent (females) such a proportion of more than 35 per cent

Calcium

As far as calcium is concerned Veiledning considers 800 mg as a high intake 600 mg as acceptable and 400 mg as a low/minimum intake The corresponding RDA 1974 figure is 800 mg Thus the average intake of this study was high according to Veiledning and above the RDA value The lower decentile values were not below the low/minimum value of Veiledning but fell below the RDA 1974 value by almost 300 mg

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than the RDA value in both sexes but higher than the acceptable value of Veiledning in males and higher than the low/minimum value of Veiledning in females

Thiamin

Veiledning s proposed high intake of thiamin as well as the RDA 1974 recommended intake is 0 5 mg per 1000 kcal/4 2 MJ On an average the intake fell above this recommended intake The lower decentile values fell above the acceptable value of Veiledning (0 4 mg per 1000 kcal/4 2 MJ) Four males and two females fell below this value and only one proband (a male) fell below the low/minimum value of Veiledning (0 3 mg per 1000 kcal/4 2 MJ) RDA suggest however on the basis of the works by Horwitt et al (30) and Oldham (42) who propose that older persons use thiamin less efficiently a daily intake of 1 mg even with a daily energy intake of less than 2000 kcal/8 4 MJ In the present material 15 males (8 per cent) and 50 females (27 per cent) showed a daily intake of less than 1 mg thiamin

Riboflavin

Veiledning s high acceptable and low/minimum values of riboflavin are 24 micrograms 20 micrograms and 14 micrograms per kg body weight respectively The value of RDA is 0 6 mg per 1000 kcal/4 2 MJ Thus the average intake in this study corresponded to the high intake value of Veiledning and fell well above the RDA 1974 value The lower decentile values however fell close to the low/minimum value of Veiledning and well below the RDA 1974 value In fact 61 males (33 5 per cent) and 60 females (31 9 per cent) had an intake of less

than Veiledning s acceptable value (20 µg per kg body weight) and 20 males (11 0 per cent) and 17 females (9 0 per cent) below the low/minimum value of Veiledning (14 µg per kg body weight)

Ascorbic_acid

The RDA 1974 value of ascorbic acid is 45 mg Veiledning gives the values corrected for losses during storage and preparation The high value of Veiledning is 30 mg the acceptable value 20 mg and the low/minimum value is 10 mg These figures are claimed to be comparable with the American figure (22) Intake of ascorbic acid was thus on average very high The lower decentile value was however somewhat below RDA 1974

Only about 3 per cent of the 70-year-olds were found to have such advanced physical or mental handicaps that care in hospitals nursing-homes or homes for the elderly was obviously indicated Another 2 per cent of the population needed help with activities of daily living (6) Furthermore a certain number of probands were under treatment for diseases such as cardiac insufficiency and rheumatoid arthritis which obviously must have influenced their physical activity and the need of energy and nutrients

Thirteen per cent of the 70-year-olds reported that their main mode of transportation within the city during the summer half of the year was walking or riding a bicycle This group of individuals was found to have an average dietary energy intake of 2421 kcal/10 2 MJ per day (males) and 2070 kcal/8 7 MJ (females) compared with 2328 kcal/9 8 MJ and 1911 kcal/8 0 MJ respectively in the rest of the material indicating that this group of physically relatively active people might to a certain degree have been responsible for

the right part of the distribution curve of energy intake These differences were however not statistically significant (p > 0 05 Student s t-test)

The meal pattern of the main part of the probands with at least one hot meal and one acceptable other meal per day seemed to be acceptable Our results indicate that no male proband and only 1 per cent of the females did not have at least one hot meal a day Furthermore in no probands from a nutritional aspect lesser good meals like coffee and buns seem to have been dominating the intake of energy and nutrients

Thus the average 70-year-old person in Gothenburg had apparently adequate intake of food and good dietary habits As will be reported elsewhere the body composition was found to be rather similar to that of previously investigated middle-aged individuals regarding body fat (50) The variations in intake of energy and nutrients were not greater than in an earlier investigated middle-aged group of females (10) Further detailed analyses of our results will aim at answering the question as to what extent the low intake values were shown by people with diseases in this age group

Earlier studies of dietary habits and/or intake of energy and nutrients in Sweden include i n t e r v i e w studies in elderly people living in homes for the elderly in Stockholm (52) in elderly non-institutionalized people and in pensioners living in homes for the elderly in Uppsala and surroundings (55) in i a 75-year-old women in Gothenburg (27) in people in all Sweden - up to 75 years of age (33) in elderly people living alone and in households with others in Stockholm (43) and in all Sweden - up to 70 years of age (9) Söderberg (52) Hallberg (27) and Werner and Berfenstam (55) used the 24-hour recall method and calculated the intake of energy and nutrients These three studies show lower values of intake of energy than the present

study The non-response group was as large as 43 per cent in the 75-year-old group in the study by Hallberg (27) In the studies by Johansson (33) and Arvidsson et al (9) emphasis was laid on description of meal habits and meal composition expressed in terms of food groups but data for the comparison of intake of energy and nutrients with the present study are not available

People with dentures in both jaws at the average age of 65 have been studied in the town of Umeå in northern Sweden with the 7 - d a y d i e t a r y r e c o r d technique (53) The energy intake was on average lower (males 7 7 MJ females 6 3 MJ) than in the present study It is tempting to interpret the difference between their data and the present data as a difference dependent on differences in chewing ability in the two samples A comparison of energy intake in people with different dental state (evaluated by Tor Österberg DDS) in the present study showed however that the dental state influenced the choice of food but not significantly the intake of energy (29)

Elderly people in a rural district in southern Sweden (Dalby) have been studied with the d u p l i c a t e p o r t i o n technique (1 2 3 6 14 26 45) which has apparently given systematically lower values of intake of energy and nutrients than the present study - for a discussion of methodological differences between the duplicate portion technique and the dietary history method see (51) The constantly lower figures for intake of energy and nutrients with the duplicate portion technique might be due to difficulties for the probands to really maintain their ordinary food habits during the artificial experimental situation in which just as much food as that eaten is taken away for chemical analyses

Outside Scandinavia certain nutrition studies have been performed in industrial countries with a social

structure and a climate not too different from that of Sweden - for a review see (19) The comprehensive study performed in U K 1967-68 by the Panel on Nutrition of the Elderly (44) was mainly based on the 7-day record method Unfortunately that study suffered from a non-response rate of on average 44 per cent and in certain regions of as much as 68 per cent of the numbers drawn in the samples Certain comparisons of responders and non-responders and analyses of the representativity of the response group were performed In areas with a lower non-response rate (e g Rutherglen with a non-response rate of 19 per cent) the observed energy intake was in the same order of magnitude (2320 kcal/9 7 MJ) for males but seemed to be lower (1735 kcal/7 3 MJ) for females compared to the present study

In another nutrition survey in U K performed in 1969-1972 on 77 men and 187 women over the age of 65 and living at home (38 39 40) the mean intake of energy was 2300 kcal/9 7 MJ for men and 1750 kcal/7 3 MJ in women The non-response rate was however about 30 per cent and analyses of the representativity of the participants were not reported The limited possibilities of comparisons of nutritional data between only age based samples are illustrated by e g that height and weight of the 65-74 year-old males in that study were 166±5 (M±SD) cm and 67±14 kg which are approximately 7 cm shorter and 9 kg less than the 70-year-olds in Gothenburg The English women aged 65-74 years had a body weight of 64±10 kg and a height of 152±7 cm which means that they were of about the same body weight but approximately 8 cm shorter than the 70-year-old females in Gothenburg

In Gothenburg there are possiblities for comparisons of nutritional data between individuals in different ages in the same urban area These comparisons can only be made at present on a cross-sectional and not

on a longitudinal basis A comparison between this study and studies on e g middle-aged women in Gothenburg shows that the energy intake (10) and the body composition (49) in females is in the same order of magnitude in these two groups as far as can be judged from cross-sectional studies

This might mean that the physical activity of the 70-year old female is on an average similar to that of middle-aged females in Gothenburg If the capacity of the elderly to utilize food is lower than in middle-aged women a change in the relationship between body fat and body cell mass should have been demonstrated The body cell mass calculated from measurements of total body potassium does not seem to be lower in 70-year-old females than in middle-aged women (49) However ageing per se in fact might cause a gradual decrease in body cell mass as proposed in earlier studies (7 16 25 41 48) The apparently same amount of body cell mass in females at the age of 70 and in middle life found in these cross-sectional studies might then be a result of selective mortality between these ages and/or secular factors

Our conclusions concerning dietary habits in the 70-year-olds are thus in good agreement with the overall impression from the population study 70-year-old people in Gothenburg that this age group in general comprises individuals with rather good health

REFERENCES

1 Abdulla M Andersson I Jägerstad M & Nair B Kostundersökning med dubbelportionsteknik bland pensionärer i Dalby - proteiner och aminosyror In Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 235 Astra Södertälje 1976

2 Abdulla M Jägerstad M & Svensson S : Kostundersökning med dubbelportionsteknik bland pensionärer i Dalby - kalcium magnesium zink In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 248 Astra Södertälje 1976

3 Abdulla M Jägerstad M & Svensson S Kostundersökning med dubbelportionsteknik bland pensionärer i Dalby - natrium och kalium In Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 251 Astra Södertälje 1976

4 Abramson E : Kosttabell 5th edition Läromedelsförlagen Stockholm 1971

5 Abu-Erreish G Neely J R Whitmer J T Whitman V & Sanadi D R Studies on fatty acid oxidation by isolated perfused working hearts of aged rats Congress Abstracts volume I:100 10th International Congress of Gerontology Jerusalem Israel June 22-27 1975

6 Åkesson B Andersson I Borgström B & Nilsvik M -B : Kostundersökning med dubbelportionsteknik bland pensionärer i Dalby - intag av fett och steroler In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 237 Astra Södertälje 1976

7 Allen T H Anderson E C & Langham W H : Total body potassium and gross body composition in relation to age J Gerontol 15:348 1960

8 Andersson E Lawenius M Persson C Rinder L Steen B & Svanborg A : Classification diagnosis and treatment of mental diseases in the elderly Age and Ageing Suppl issue 64 1975

9 Arvidsson O Jonsson E Skerfving S & Stütz G : Kost och motion i Sverige Socialstyrelsen Allmänna Förlaget Stockholm 1973

10 Arvidsson Lenner R Bengtsson C Carlgren C Isaksson B Lundgren B K Petersson I & Tibblin E The study of women in Gothenburg 1968-1969 Intake of energy and nutrients in women of five different age groups Acta med scand In print 1977

11 Barrows C H : Enzymes in the study of biological aging In: Perspectives in experimental gerontology (ed N W Shock) p 169 Charles C Thomas Springfield Ill 1966
12 Björn-Rasmussen E Hallberg L & Walker R B : Food iron absorption in man I Isotopic exchange between food iron and inorganic iron salt added to food studies on maize wheat and eggs Am J Clin Nutr 25:317 1972
13 Blomhoff J P Serum cholesterol determination by gas-liquid chromatography Clin chim Acta 43 257 1973
14 Borgström B Andersson I Dahlqvist A Dencker I Nordén Å & Åkesson B : Kostundersökning med dubbelportionsteknik bland pensionärer i Dalby - energiintag In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 233 Astra Södertälje 1976
15 Burke B S : The dietary history as a tool in research J Am Diet Ass 23:1041 1947
16 Burmeister W & Bingert A : Die quantitativen Veränderungen der menschlichen Zellmasse zwischen dem 8 und 90 Lebensjahr Klin Wochenschr 45 409 1967
17 Carlson L A & Wadström L : Determination of glycerides in blood serum Clin chim Acta 4:197 1959
18 Chen J C Warshaw J B & Sanadi D R : Regulation of mitochondrial respiration in Senescence J Cell Phys 80 141 1972
19 Durnin J V G A : Nutrition In: Textbook of Geriatric Medicine (ed J C Brocklehurst) p 384 Churchill Livingstone Edinburgh and London 1973
20 Durnin J V G A & Passmore R : Energy work and leisure Heinemann London 1967
21 Edwards D A W Hammond W H Healy M J R Tanner J M & Whitehouse R H : Design and accuracy of calipers for measuring subcutaneous tissue thickness Brit J Nutr 9 133 1955
22 Eeg-Larsen N Isaksson B Nicolaysen R & Wretlind A : Veiledning til vurdering og planlegging av kosthold Landforeningen for kosthold og helse Universitetsforlaget Oslo 1971
23 FAO/WHO Energy and protein requirements Wld Hlth Org techn Rep Ser No 522 1973
24 Food and Nutrition Board Recommended Dietary Allowances 8th edition National Academy of Sciences Washington D C 1974
25 Forbes G B & Reina J C : Adult lean body mass declines with age some longitudinal observations Metabolism 19 653 1970
26 Haglund G & Nordén Å : Hälsotillståndet hos 37 pensionärer i Dalby vars kost undersökts med dubbelportionsteknik In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen

27 Hallberg L : Fetma hos kvinnor i olika åldrar: kaloriintag och födoämnesval Läkartidningen 63: 612 1966
28 Hansen H A : On the diagnosis of folic acid deficiency Academic thesis Orstadius Tryckeriaktiebolag Göteborg 1964
29 Hedegård B Steen B Svanborg A & Österberg, T : Oral health and dietary habits in 70-year-old males and females in Gothenburg Sweden A population study In preparation 1977
30 Horwitt M K Liebert E Kreisler O & Wittman P : Investigations of human requirements for B-Complex vitamins NRC Bull 116 p 106 National Academy of Sciences Washington D C 1948
31 Hutner S H Bach M K & Ross G I M : A sugar-containing basal medium for vitamin B_{12}-assay with Euglena application to body fluids J Protozool 3 101 1956
32 Härtel A Helger R & Lang H Die Blutzuckerbestimmung mit der o-Toluidin-Methode ohne Eisessig Z Klin Chem Klin Biochem 7 14 1969
33 *Johansson S Den vuxna befolkningens kostvanor* Allmänna Förlaget Stockholm 1971
34 Judge T G & Cowan N R : Dietary potassium intake and grip strength in older people Geront clin *13:221 1971*
35 Lillienberg L & Svanborg A Determination of plasma cholesterol comparison of gas-liquid chromatographic colorimetric and enzymatic analyses *Clin chim Acta 68:223 1976*
36 Lindberg W Natvig H Rygh A & Svendsen K : Høyde- og vektundersøkelser hos voksne menn og kvinner Forslag til nye norske høyde-vektnormer *Tidsskr Norske Laegefor 76 361 1956*
37 Lonergan M E Milne J S & Williamson J : Physical activity and energy expenditure of elderly men and women in Edinburgh Scotland Geront *Clin 15 113 1973*
38 MacLeod C C Judge T G & Caird F I : Nutrition of the elderly at home I Intakes of energy protein carbohydrates and fat Age and Ageing 3 158 1974
39 MacLeod C C Judge T G & Caird F I : Nutrition of the elderly at home II Intakes of Vitamins Age and Ageing 3:209 1974
40 MacLeod C C Judge T G & Caird F I Nutrition of the elderly at home III Intakes of minerals Age and Ageing 4 49 1975
41 Novak L P Aging total body potassium fat-free mass and cell mass in males and females between ages 18 and 85 years J Gerontol 27 438 1972
42 Oldham H G : Thiamine requirements of women Ann N Y Acad Sci 98 542 1962
43 Olin R : Äldre stockholmares hälsotillstånd Thesis Stockholm 1971

44 Panel on Nutrition of the Elderly: A nutrition survey of the elderly Department of Health and Social Security Reports on Health and Social Subjects No 3 H M S O London 1972
45 Qvist I : Fostundersökning med dubbelportions-teknik bland pensionärer i Dalby - järninnehåll In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 259 Astra Södertälje 1976
46 Rinder L Roupe S Steen B & Svanborg A : 70-year-old people in Gothenburg A population study in an industrialized Swedish city I General presentation of the study Acta med scand 198:397 1975
47 Shock N W : Energy metabolism caloric intake and physical activity of the aging In Nutrition in Old Age Symposia of the Swedish Nutrition Foundation X (ed L A Carlson) p 12 Almqvist & Wiksell Uppsala 1972
48 Shukla K K Ellis K J Dombrowski C S & Cohn S H Physiological variation of total-body potassium in man Am J Physiol 224 271 1973
49 Steen B Bengtsson C Bruce Å Isaksson B & Tibblin G Kroppssammansättningen hos män och kvinnor i olika åldrar i Göteborg - resultat från tre populationsstudier In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 213 Astra Södertälje 1976
50 Steen B Bruce Å Isaksson B Lewin T & Svanborg A Body composition in 70-year-old people in Gothenburg Sweden A population study Acta med scand Suppl 611 89 1977
51 Discussion in section Fysisk aktivitet och nutrition hos de äldre In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 260 Astra Södertälje 1976
52 Söderberg S Konsumtionen av näringsämnen bland ensamstående pensionärer Socialmedicinsk Tidskrift 36:143 1959
53 Söremark R & Nilsson B Dental status and nutrition in old age In Symposium of the Swedish Nutrition Foundation X Nutrition in Old Age (ed L A Carlson) p 147 Almqvist & Wiksell Uppsala 1972
54 Thomaeus B : Konsumtionen av livsmedel m m Jordbruksekonomiska Meddelanden 179 1972
55 Werner I & Berfenstam R : The nutrient consumption and food choice of elderly people in Sweden I Annales Acta acad regiae scientiarum upsaliensis Kungl vetenskapssamhällets i Uppsala årsbok 18/1974 Almqvist & Wiksell International Stockholm 1974

56 Wiehl D G : Diets of a group of aircraft workers in southern California Milbank Mem Fund Quart 20 329 1942
57 Wretlind A : Nutrition problems in healthy adults with low activity and low caloric consumption In: Nutrition and Physical Activity Symposia of the Swedish Nutrition Foundation V (ed G Blix) p 114 Almqvist & Wiksell Uppsala 1967

BODY COMPOSITION
IN 70-YEAR-OLD MALES AND FEMALES IN GOTHENBURG SWEDEN
A POPULATION STUDY

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ABSTRACT

The objectives of this substudy within the population study 70-year-old people in Gothenburg Sweden were to determine the body composition of the probands and to clarify possible relationships between results of these body compartment determinations and more simple somatometric variables The cross-sectional data will be used as a basis for a prospective longitudinal geriatric/gerontological study The subsample comprised 66 males and 76 females of whom

females underwent a complete examination The probands examined were considered representative of the 70-year-old population in Gothenburg Total body potassium was estimated by using a whole body counter and total body water with an isotope dilution technique using tritiated water as a tracer Body cell mass intracellular and extracellular water body fat and fat-free extracellular solids were then calculated from body weight total body potassium and total body water using certain assumptions the relevance of which in this age group is discussed Average values of body weight were 76 2 kg and 66 3 kg of body cell mass 28 1 kg and 20 3 kg and of body fat 12 5 kg and 18 1 kg in males and females respectively It was possible from body weight and subscapular skinfold in males and from body weight thigh and triceps skinfold in females to reach a proportion of explained variance of body fat of 58 per cent and 76 per cent respectively There was a good correlation between body fat and the difference between body weight and ideal body weight as defined by Lindberg and collaborators 1956 A preliminary comparison between the current data and corresponding data from cross-sectional studies of middle-aged individuals in Gothenburg showed that the amount of fat was similar in the two age groups Body cell mass seemed to be of the same order of magnitude in 70-year-old as in middle-aged females but showed a lesser value in 70-year-old than in middle-aged males

INTRODUCTION

The composition of the human body reflects genetic and environmental factors such as physical activity

nutrition and certain diseases To what extent the ageing processes per se influence the body composition is only known fragmentarily but there is reason to believe that the body cell mass will decrease at higher ages (1 8 11 20 23) Furthermore changes in cardiac and renal functions that might influence the amount of body water are common in higher ages even in individuals without obvious symptoms of cardiac or renal diseases

There is reason to believe that the body composition is also of relevance to the level of different compounds in the blood such as creatinin triglycerides and free fatty acids A more detailed knowledge o the body composition is thus also of importance for a wider knowledge of the blood homeostasis of certain components especially the blood concentration of those used as an indication of the presence or absence of diseases Furthermore the d stribution of certain drugs depends to some extent on the relative size of the different body compartments that might influence drug tolerance

Determinat on of body composition in higher ages has thus not only a general gerontological interest but also importance f om many geriatric aspects

The aim of the present study was to determine body compos tion in a Swedish population of 70-year-old people The study is on the one hand a part of a broad gerontological/geriatric investigation of social and medical conditions of this age group (21) and on the other a part of a systematic survey of dietary habits and body composition in different age groups in Gothen bu g (3 25 26) The objectives were also to clarify pos ible relationships between results of body compartment determinations with isotope techniques and more simple somatometric variables

MATERIAL

The general design of the population study - the total sample comprised 1148 70-year-old persons (521 males and 627 females) - the sampling procedure analysis of the non-response and a broad presentation of investigation procedures have been presented earlier (21)

The subsample chosen for the body composition study was composed of those probands who underwent the examination programme at the hospital during the period February 14th to May 26th and September 11th to September 22nd 1972 as well as the dietary survey This subsample comprised 142 probands (66 males and 76 females) 59 males and 62 females actually took part in the study which means a non-response rate of 11 per cent in males and 18 per cent in females The causes of non-response are given in Table I Furthermore in 10 males and 6 females the examination was considered incomplete or technically unsuccessful on the basis of the criteria reported later on

Table I Causes of non-response

	Males	Females
Refusal	2	8
Severe illness	4	2
Institutional care outside Gothenburg	1	3
Claimed claustrophobia	0	1

Thus 49 males and 56 females were considered to have undergone a complete examination and the results are based on data on these probands

In order to test the representativity of the examined probands they were compared with other propositi in the study regarding sex marital status proportion of male probands registered in the Register of Temperance Board income and community rent allowances and with other probands in the study regarding height body weight waist girth triceps skinfold and subscapular skinfold (Table II) There were no significant differences on the one per cent level (x^2-test and Student s t-test respectively) in these respects between the examined group and other propositi and probands respectively

METHODS

Body composition data were calculated from measurements of body weight (BW) total body potas ium (TBK) and total body water (TBW)

T o t a l b o d y p o t a s s i u m was estimated by using a high sensit vity whole body counter utilizing plasti scintillators (24) to detect the gamma radiation from the naturally occurring radionuclide ^{40}K which is a constant fraction of all natural potassium The counter had been calibrated by the administration of ^{42}K to vol ntee s This calibration is described elsewho e (2) The total expected standard d viation of a s ngle potassium determination is approximately 80 mmol including random e rors due to

Table II Average values of ıeight body weight waist girth triceps and subscapular skinfold in those probands in whom body composition was examined and in other probands (Student s t-test NS: p >0 05)

	Males			Females		
	Examined	Not examined	Sign	Examined	Not examined	Sign
	n=49	n=402		n=56	n=466	
Height (cm)	173	174	NS	160	160	NS
Body weight (kg)	76 2	76 2	NS	66 3	66 8	NS
Waist girth (cm)	90 4	89 7	NS	82 3	83 3	NS
Triceps skinfold (mm)	9 2	8 6	NS	20 0	18 2	p<0 05
Subscapular skinfold (mm)	15 4	14 3	NS	17 5	18 0	NS

the counting statistics calibration uncertainties and uncontrollable variations in the measuring procedures The subjects were asked to bath and wash their hair the day before the measurement during which they were dressed in underwear and a hospital gown previously checked to contain no radioactive contamination The count duration for each subject was 100 seconds

T o t a l b o d y w a t e r was determined with an isotope dilution technique using tritiated water (THO) as a tracer (5 17) 400 µCi THO was given perorally and was equilibrated for five hours The specific activity (THO/H_2O) in urine was calculated from measurements of two consecutive voidings two hours apart collected after the bladder had been emptied at the end of the equilibrium period The urine samples were distilled on a sand-bath Of the colour-free distillate 0 5 ml was mixed in duplicate with 10 ml of a scintillation liquid (200 g Naphtalene 25 g PPO 100 mg POPOP in 2000 ml Dioxane) and measured in a liquid scintillation counter (Tri-Carb Packard Instruments Co) Such determinations were rejected where only one urine sample was available or where the difference in specific activity between the two samples exceeded 10%

C a l c u l a t i o n s Most of the body potassium (about 98 per cent) is located intracellularly and was during the calculations considered to be in constant relation with the cell mass The water content of the body cells was also considered to be constant It was thus possible to estimate body compartments from determinations of BW TBF and TBW

Body cell mass (BCM) in kg was calculated as TBK (in mmol) x 8 33 x 10^{-3} (19) Intracellular water (ICW) in kg was calculated as 78 per cent of BCM Extracellular water (ECW) in kg was calculated as TBW-ICW Body fat (BF) in kg was calculated as BW-(BCM+ECW+FFECS) where FFECS (fat-free extracellular solids) were approximated at 12 per cent of BW (5 17)

Table II Average valucs of ıeight body weıght waist girth triceps and subscapular skinfold ın those probands ın whom body composıtıon was examined and in other probands (Student s t-test NS: p >0 05)

	Males			Females		
	Examined n=49	Not examined n=402	Sign	Examined n=56	Not examined n=466	Sign
Height (cm)	173	174	NS	160	160	NS
Body weight (kg)	76 2	76 2	NS	66 3	66 8	NS
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Triceps skinfold (mm)	9 2	8 6	NS	20 0	18 2	p<0 05
Subscapular skinfold (mm)	15 4	14 3	NS	17 5	18 0	NS

- subject standing The mean difference between the two observers was -4 0±0 5 mm (M±SE)

None of the above mentioned differences differed significantly ($p > 0$ 05 Student s t-test) from zero

When studying correlations to body fat the difference between BW and ideal body weight was used The ideal body weight in kg was calculated for males as (height in cm x 0 71)-53 9 and for females as (height in cm x x 0 67)-48 1 from the data of Lindberg et al (16)

R e l a t i o n a n a l y s e s In order to analyze the possible relation between the results and certain characteristics of the probands the following dicotomic contrast groups were studied regarding the body composition data:

I <u>Diuretic treatment</u> Probands with (6 males and 18 females) contra probands without (43 males and 38 females) diuretic treatment (thiazides other diuretic sulfonamide compounds or ethacrynic acid)

II <u>Congestive heart failure</u> Probands with (14 males and 7 females) contra probands without (35 males and 49 females) congestive heart failure (two of the symptoms oedema cyanosis and dyspnoe at the general medical examination and a calculated heart volume of 500 ml per m^2 body surface or more (males) and 450 ml per m^2 body surface (females) respectively and/or three of those symptoms and/or digitalis treatment and heart volume as above and/or heart volume as above in absence of hypertension (see below) and/or congestion of the pulmonary vessels judged by the roentgenologist)

III <u>Hypertension</u> Probands with (7 males and 20 females) contra probands without (42 males and 36 females) hypertension (treatment with antihypertensive drugs and/or a diastolic blood pressure of 115 mm Hg or more and/or anamnestic hypertension and a heart volume as above in absence of congestive heart failure (see II)

S k i n f o l d measurements were performed with a Harpenden caliper (10) with a pressure of 10 g/mm^2 applied at a contact surface of 20 mm^2 The skinfold was measured 1) at the back of the right upper arm midway between acromion and elbow with the arm hanging relaxed and with the fold running parallel to the length of the arm - subject standing - (triceps skinfold) 2) just below the angle of the right scapula with the fold parallel to the natural cleavage line of the skin - subject standing - (subscapular skinfold) 3) just above the right anterior superior iliac spine with the fold parallel to the natural cleavage line of the skin - subject in supine position - (suprailiac skinfold) and 4) at the front of the right thigh midway between groin and patellar base with the fold vertical - subject standing with slight flexion in the hip and knee joints (thigh skinfold) Triceps and subscapular skinfolds were measured on all probands by one and the same registered nurse who was specially trained for the purpose Three measurements were taken at each position and the results were based on the average value of these observations Suprailiac and thigh skinfolds were measured - one observation per measured proband - in a subsample (n=329) including those probands who underwent the body composition study by two observers (one of us /T L / and a specially trained technician) An inter-observer variation study in these two observers revealed a mean difference of -0 2±0 3 mm (M±SE) and -0 5±0 5 mm for suprailiac and thigh skinfolds respectively

U p p e r a r m g i r t h was measured over the midpoint of head of the right biceps muscle - subject standing with upper arm slightly abducted and elbow flexed at 90^{0} The mean difference between the two observers was -1 0±1 0 mm (M±SE)

W a i s t g i r t h was measured horizontally halfway between the lowest floating ribs and iliac crests

- subject standing The mean difference between the two observers was -4 0±0 5 mm (M±SE)

None of the above mentioned differences differed significantly (p > 0 05 Student s t-test) from zero

When studying correlations to body fat the difference between BW and ideal body weight was used The ideal body weight in kg was calculated for males as (height in cm x 0 71)-53 9 and for females as (height in cm x x 0 67)-48 1 from the data of Lindberg et al (16)

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III <u>Hypertension</u> Probands with (7 males and 20 females) contra probands without (42 males and 36 females) hypertension (treatment with antihypertensive drugs *and/or* a diastolic blood pressure of 115 mm Hg or more *and/or* anamnestic hypertension and a heart volume as above in absence of congestive heart failure (see II)

S k i n f o l d *measurements were performed* with a Harpenden caliper (10) with a pressure of 10 g/mm^2 applied at a contact surface of 20 mm^2 The skinfold was measured 1) at the back of the *right upper arm* midway between acromion and elbow with the arm hanging relaxed and with the fold running parallel to the length of the arm - subject standing - (triceps skinfold) 2) just below the angle of the right scapula with the fold parallel to the natural cleavage line of the skin - subject standing - (subscapular skinfold) 3) just above the right anterior superior iliac spine with the fold parallel to the natural cleavage line of the skin - subject in supine position - (suprailiac skinfold) and 4) at the front of the right thigh midway between groin and patellar base with the fold vertical - subject standing with slight flexion in the hip and knee joints (thigh skinfold) Triceps and subscapular skinfolds were measured on all probands by one and the same registered nurse who was specially trained for the purpose Three measurements were taken at each position and the results were based on the average value of these observations Suprailiac and thigh skinfolds were measured - one observation per measured proband - in a subsample (n=329) including those probands who underwent the body composition study *by two observers (one of us /T L / and a specially* trained technician) An inter-observer variation study in these two observers revealed a mean difference of -0 2±0 3 mm (M±SE) and -0 5±0 5 mm for suprailiac and thigh skinfolds respectively

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IV <u>Prostatic enlargement and/or prostatism</u> Male probands with (n=15) contra male probands without (n=34) prostatic enlargement judged by the physician at the general medical examination <u>and/or</u> symptoms of prostatism based on clinical evaluation of anamnestic data

V <u>Urinary infection</u> Female probands with (n=6) contra females without (n=50) urinary infection (positive or doubtful result from first Cultube® test - for bacteriuria - <u>and</u> positive result from a second Cultube® test)

RESULTS

Waist girth triceps skinfold and subscapular skinfold are given in Table II In the body composition examined subsample upper arm girth was 294±22 3 mm (M±SD) and 299±36 7 mm suprailiac skinfold 13 9±6 61 mm and 19 9±8 77 mm and thigh skinfold 17 0±10 2 mm and 27 9± ±11 0 mm in males and females respectively

Height BW TBW and TBK are given in Table III TBW constituted on an average 63 per cent of BW in males and 54 per cent in females The different body composition data is calculated both in absolute and relative terms (related to BW) in Table IV The mean ratio between ECW and ICW was 1 21 in males and 1 27 in females Average BCM and ECW were both more than twice as great as average BF in males whilst in females all these three compartments were of the same order of magnitude

The correlation coefficients between BW BCM ECW and BF versus different anthropometric measurements are

Table III Average values of height body weight (BW) total body water (TBW) and total body potassium (TBK) SD: standard deviation

	Males (n=49)		Females (n=56)	
	Mean	SD	Mean	SD
Height (cm)	173	5 9	160	6 0
BW (kg)	76 2	11 1	66 3	12 4
TBW (kg)	48 1	6 5	35 8	5 5
TBK (mmol)	3360	422	2433	323

Table IV Average values of body cell mass (BCM) extracellular water (ECW) and body fat (BF) in absolute values and in per cent of body weight (BW) SD: standard deviation

	Males		Females	
	Mean	SD	Mean	SD
Absolute values (kg)				
BCM	28 1	3 5	20 3	2 7
ECW	26 5	5 0	20 0	4 3
BF	12 5	6 5	18 1	7 2
Relative values (per cent of BW)				
BCM	37 1	4 0	30 9	4 0
ECW	34 9	5 6	30 2	4 9
BF	16 1	7 0	26 6	6 7

IV <u>Prostatic enlargement and/or prostatism</u> Male probands with (n=15) contra male probands without (n=34) prostatic enlargement judged by the physician at the general medical examination <u>and/or</u> symptoms of prostatism based on clinical evaluation of anamnestic data

V <u>Urinary infection</u> Female probands with (n=6) contra females without (n=50) urinary infection (positive or doubtful result from first Cultube® test - for bacteriuria - <u>and</u> positive result from a second Cultube® test)

RESULTS

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Height BW, TBW and TBK are given in Table III TBW constituted on an average 63 per cent of BW in males and 54 per cent in females The different body composition data is calculated both in absolute and relative terms (related to BW) in Table IV The mean ratio between ECW and ICW was 1 21 in males and 1 27 in females Average BCM and ECW were both more than twice as great as average BF in males whilst in females all these three compartments were of the same order of magnitude

The correlation coefficients between BW BCM ECW and BF versus different anthropometric measurements are given in Tables V-VI

Table VI Correlation coefficients between body weight (BW) body cell mass (BCM) extracellular water (ECW) body fat (BF) and other variables females (S: significance from zero xxx $p < 0\ 001$ xx $p < 0\ 01$ x: $p < 0\ 05$ NS: $p > 0\ 05$)

	Females							
	BW		BCM		ECW		BF	
	r	S	r	S	r	S	r	S
Height	0 40	xx	0 35	xx	0 47	xxx	0 19	NS
Body weight	-		0 69	xxx	0 66	xxx	0 83	xxx
Body cell mass	0 69	xxx		-	0 38	xx	0 44	xxx
Extracellular water	0 66	xxx	0 38	xx	-	-	0 26	x
Body fat	0 83	xxx	0 44	xxx	0 26	x	-	-
Upper arm girth	0 86	xxx	0 64	xxx	0 66	xxx	0 67	xxx
Waist girth	0 85	xxx	0 52	xxx	0 57	xxx	0 75	xxx
Triceps skinfold	0 69	xxx	0 48	xxx	0 51	xxx	0 56	xxx
Subscapular skinfold	0 67	xxx	0 51	xxx	0 26	x	0 67	xxx
Suprailiac skinfold	0 64	xxx	0 42	xx	0 38	xx	0 59	xxx
Thigh skinfold	0 50	xxx	0 30	x	0 10	NS	0 57	xxx

Table V Correlation coefficients between body weight (BW) body cell mass (BCM) extracellular water (ECW) body fat (BF) and other variables males (S: significance from zero xxx: $p < 0\ 001$ xx: $p < 0\ 01$ x: $p < 0\ 05$ NS: $p > 0\ 05$)

	Males							
	BW		BCM		ECW		BF	
	r	S	r	S	r	S	r	S
Height	0 61	xxx	0 63	xxx	0 41	xx	0 27	NS
BW	-	-	0 68	xxx	0 60	xxx	0 69	xxx
BCM	0 68	xxx	-	-	0 41	xx	0 16	NS
ECW	0 60	xxx	0 41	xx	-	-	-0 09	NS
BF	0 69	xxx	0 16	NS	-0 09	NS	-	-
Upper arm girth	0 74	xxx	0 51	xxx	0 40	xx	0 53	xxx
Waist girth	0 84	xxx	0 45	xxx	0 47	xxx	0 66	xxx
Triceps skinfold	0 46	xxx	0 05	NS	0 27	NS	0 47	xxx
Subscapular skinfold	0 56	xxx	0 04	NS	0 23	NS	0 65	xxx
Suprailiac skinfold	0 64	xxx	0 23	NS	0 34	xx	0 58	xxx
Thigh skinfold	0 58	xxx	0 31	x	0 34	xx	0 44	xx

Table VII Multiple regression analysis Dependent variable: body fat Independent variables: body weight (BW) waist girth (WG) triceps skinfold (TSF) subscapular skinfold (SubSF) suprailiac skinfold (SupraSF) and thigh skinfold (ThSF)

Males		Females	
Variables taken into the analysis	R	Variables taken into the analysis	R
BW	0 69	BW	0 83
BW SubSF	0 76	BW ThSF	0 85
BW SubSF TSF	0 77	BW ThSF TSF	0 87
BW SubSF TSF WG	0 78	BW ThSF TSF SubSF	0 88
BW SubSF TSF WG SupraSF	0 78	BW ThSF TSF SubSF WG	0 88
BW SubSF TSF WG SupraSF ThSF	0 78	BW ThSF TSF SubSF WG SupraSF	0 88

All parameters showed highly significant correlations to BW The highest figures (r > 0 80) were obtained for waist girth in males and upper arm girth waist girth and BF in females

Fewer parameters showed high correlations to BCM The highest figures (r > 0 60) were obtained for - apart from BW - height in males and upper arm girth in females

The correlations to ECW were also weaker than to BW Correlation coefficients higher than r=0 60 were - apart from BW in females - only obtained for upper arm girth in females

The correlations to BF were higher in females than in males regarding BW waist girth upper arm girth thigh skinfold triceps skinfold and BCM Regarding subscapular and suprailiac skinfolds the correlations were of the same order of magnitude in both sexes

The correlation coefficient between BF and the difference between BW and ideal body weight (16) was r=0 71 in males and r=0 91 in females The regression equation was BF=0 46(BW- ideal body weight)+9 4 in males and BF=0 54(BW- ideal body weight)+14 5 in females

The result of a multiple regression analysis with BF as the dependent variable is given in Table VII For both sexes BW was the most important independent variable with a R-value of 0 69 in males and 0 83 in females In males R increased to R=0 76 when subscapular skinfold (SubSF) was also taken into consideration In females the R-value was 0 87 if thigh skinfold (ThSF) and triceps skinfold (TSF) were also taken into account The regression equation after two analysis steps in males was BF (in kg)=0 28BW (in kg) +0 51 SubSF (in mm)-16 3 The corresponding equation after

Table VII Multiple regression analysis Dependent variable: body fat Independent variables body weight (BW) waist girth (WG) triceps skinfold (TSF) subscapular skinfold (SubSF) suprailiac skinfold (SupraSF) and thigh skinfold (ThSF)

Males: Variables taken into the analysis	R	Females: Variables taken into the analysis	R
BW	0 69	BW	0 83
BW SubSF	0 76	BW ThSF	0 85
BW SubSF TSF	0 77	BW ThSF TSF	0 87
BW SubSF TSF WG	0 78	BW ThSF TSF SubSF	0 88
BW SubSF TSF WG SupraSF	0 78	BW ThSF TSF SubSF WG	0 88
BW SubSF TSF WG SupraSF ThSF	0 78	BW ThSF TSF SubSF WG SupraSF	0 88

three analysis steps in females was BF (in kg) = 0 49 BW (in kg) + 0 16 ThSF (in mm) - 0 30TSF (in mm) - 13 6

With the analysis of possible relations between the body composition data and other data concerning these 70-year-olds namely the presence of diuretic treatment congestive heart failure *hypertension prostatic enlargement/prostatism* and urinary infection a low-grade *significant* difference was obtained with only one comparison; congestive heart failure in females Regarding TBW slightly higher values in both sexes were obtained in congestive heart failure but the difference was thus only statistically significant (p < 0 05 Student s t-test) in females (Table VIII)

Table VIII *Average body weight (BW) total body water* (TBW) and total body potassium (TBK) in probands with cardiac decompensation (A) and in other probands (B) *(Student s t-test NS:p > 0 05)*

	Males			Females		
	A (n=14)	B (n=35)	Sign	A (n=7)	B (n=49)	Sign
BW	78 8	75 1	NS	73 9	65 2	NS
TBW	50 6	47 5	NS	40 1	35 2	p<0 05
TBK	3410	3352	NS	2569	2415	NS

As in the tests of representativity of the examined group no significant differences at the one per cent level were obtained between the examined subsample and other propositi and probands respectively the examined group seemed to be representative for the total material As shown earlier in detail (21) the total material was also generally representative of 70-year-old people in Gothenburg

Total body water and total body potassium have been previously studied in higher age groups Calculations of body fat on the assumptions used in this study have only been performed previously in studies of younger age groups One may question whether the assumptions which the calculations of the body composition were based on are correct in the present age group

One possibility may be that the amount of fat-free extracellular solids has decreased due to the ageing of the bone mass Durnin and Womersley (9) have compiled data from different investigations using a variety of experimental techniques They found the amounts of skeletal bone reported to be 8 to 15 per cent lower in 75-year-old than in 50-year-old males and about 18 per cent to 30 per cent lower in 75-year-old than in 45-year-old females

If the average loss of bone from middle age is roughly estimated to be 10 per cent in males and 25 per cent in females this would make a small but significant change in the overall gross weight of the skeleton With the calculation of body fat this would cause a false low value On the other hand it is possible that the amount of extracellular connective tissue

increases at higher ages which means that the proportion of fat-free extracellular solids might be augmented in higher age groups To what extent this might with the calculations compensate for the above-mentioned loss of fat-free extracellular solids in bone tissue is hard to predict The fact that more than 3/4 of FFECS are present in the skeleton (19) indicates however that small variations in collagen concentration and collagen amount in other organs in the body should not markedly influence the results If no such compensation existed the error of the present estimation of BF should however not exceed an average order of magnitude of 1 kg in males with a body weight of 76 kg and 2 kg in females with a body weight of 66 kg Thus on average the method might apparently underestimate the amount of body fat in males by about 8 per cent of 12 5 kg and in females by about 10 per cent of 18 kg

Another possibility might be that the factors used for the calculations of body cell mass and intracellular water i e 120 mmol potassium and 780 g water per kg cell mass are not valid for aged subjects The estimation of these factors is in general based on data on healthy young or middle-aged individuals Older rats have been shown to have a lower intracellular potassium concentration (12 14) than younger animals However available data on healthy subjects supports the opinion that the factors are just as valid at higher ages as in younger ones (6 19 28) Furthermore a similar intracellular potassium concentration has been found (7) in old patients with senile dementia

Intracellular potassium concentration is decreased in some clinical disorders and medical treatment i e starvation (15) None of the participants in the present material suffered from such conditions However not all probands were healthy 21 probands were judged to have congestive heart failure and 27 probands to

have hypertension conditions which might be suspected to be related to changes in the amount of TBW Furthermore diuretic treatment present in 6 of these males and 18 of these females might influence total body potassium and body water Only congestive heart failure in females was however found to have a slight influence on the variables studied with an increased TBW

Fifteen of the males in the present material were judged to have prostatic enlargement and/or prostatism and 6 females to have urinary infection conditions which might be suspected to cause some residual urine This might influence the results since bladder urine does not equilibrate with body water as fast as other compartments do regarding tritiated water (5) Urine samples taken for analysis might thus have been diluted with residual urine with a lower specific activity These persons were however included in the material since the difference in specific activity between the two urine portions did not exceed 10 per cent In these persons no influence on the body composition data was observed with the statistical analysis of the differences between these probands and the rest of the examined probands It should however be noticed that 3 of the 4 female probands whose TBW determinations were rejected due to a difference in specific activity between the two urine samples exceeding 10 per cent suffered from conditions that might be combined with an incomplete emptying of the bladder at the end of the equilibrium period (one female had been treated with radiation for cancer of the uterus another had had an operation for a prolaps of the uterus and the third had a urinary infection) The possible limitation of the methods used for analysis of body composition in individuals in whom a residual urine is present should be taken into consideration In those 10 males in whom the determination was rejected the production of only one urine sample was the reason for rejection in all cases but 3 in whom no obvio[illegible]

increases at higher ages which means that the proportion of fat-free extracellular solids might be augmented in higher age groups To what extent this might with the calculations compensate for the above-mentioned loss of fat-free extracellular solids in bone tissue is hard to predict The fact that more than 3/4 of FFECS are present in the skeleton (19) indicates however that small variations in collagen concentration and collagen amount in other organs in the body should not markedly influence the results If no such compensation existed the error of the present estimation of BF should however not exceed an average order of magnitude of 1 kg in males with a body weight of 76 kg and 2 kg in females with a body weight of 66 kg Thus on average the method might apparently underestimate the amount of body fat in males by about 8 per cent of 12 5 kg and in females by about 10 per cent of 18 kg

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Table IX Total body potassium per kg body weight from different studies Reference 1 21 24 present study: mean values Reference 8: median values

Reference	Age (ys)	Males		Females	
		Number	mmol K/ kg BW	Number	mmol K/ kg BW
1	58-68	30	45 1[a]		
	60-67			18	32 6[a]
	70-85	4	43 1[a]		
	78-79			3	34 2[a]
8	65-70	185	43 7[b]	144	32 8[b]
	70-75	97	43 1[b]	44	31 6[b]
21	55-65	42	47 8	54	38 2
	65-85	18	43 4	13	37 6
24	60-65	21	40 7[c]		
	60-70			5	31 5[c]
present study	70	49	44 1	56	36 7

a) calculated from values given for BW and total potassium

b) calculated from values given for BW and cell mass Potassium concentration stated to be 92 5 mmol/kg cell mass

c) calculated from values given in diagrams

urine samples was found

The whole body counter has been used for estimating the total body potassium in different populations and cross-sectional data has been presented from e g Los Alamos New Mexico (1) Rochester Minnesota (20), Brookhaven New York (23) and Germany (8) As seen from Table IX the data from these studies and our studies expressed as mmol TBK per kg BW generally agree well The only exception is the data from Brookhaven which is slightly lower than ours and the data from the other centres mentioned

Some cross-sectional data on the total body water of the aged human has been published (13 19) Our figures for the relative amount of total body water are higher than those from U K (13) and U S A (19) The explanation may be that individuals in the material from U K and U S A were generally somewhat fatter than their counterparts in Gothenburg That Swedish people may have a lower amount of body fat than people in U K and U S A is supported by comparisons of BW/height measurements and skinfold measurements in studies from these two countries (9 18 22) and the present material

Differences in the results of body composition analyses between the studies mentioned and the present study might also at least to some extent be explained by different epidemiological sampling techniques To what extent the above mentioned studies were performed as representative samples of the population is not clear

Further observations that came out of this study were that males still at the age of 70 years had a higher relative amount of body cell mass than females and a slightly higher amount of extracellular water whilst their amount of body fat was almost only half of that

its relation to body fat This ideal weight was based mainly on measurements on young and middle-aged individuals and the age range covered individuals up to 69 years That material was not representative of the total population as it only covered individuals with working capacity and employed in e g different industries As far as we know the present study is the first that concerns a representative sample of a higher age population There was a rather good correlation between body fat and the difference between body weight and the ideal weight Regression equations with body fat as the dependent and body weight and ideal body weight as independent variables were obtained which might be used in practical clinical work

Epidemiological body composition studies have also been performed on younger populations in Gothenburg A detailed comparison between the present data and data from the other studies cannot yet be performed as the complete basal data from these studies has not been published as yet However a preliminary comparison (25) with 54-year-old males (27) and females (4) shows that the amount of body fat was roughly the same in these two age groups Body cell mass was lower in 70-year old males than in 54-year-old males but similar n females One possible explanation might be that ret red males at the age of 70 have a lower physical activ ty than n active middle-life and therefore have lowe muscle mass The same amount of body fat in the two male age groups might be a result of a decrea ed intake of energy In females the data might be consistent with the hypothesis that both physical ctivity and energy intake are of the same order of magnitude n the two age groups

However comparisons between cross-sectional studies must be interpreted with great caution An apparent change of a variable between two age groups might be

of the females Contrary to younger people the ECW/ICW ratio was the same in both sexes in the present material and well above 1

It is hard to explain the sex difference regarding the correlation between BCM and BF (r=0 16 and r=0 44 for males and females respectively) Obviously the obese male might have a less developed muscle mass than the obese female Still harder to explain is the relatively low correlation between BCM and height in females (r=0 35)

The determination of the body composition by whole-body counting and isotope dilution is a simple and reliable method and with a minimum of inconvenience to the patient It has one drawback however The whole-body counter is only available at a few centres One major aim of the present study therefore was to test whether any calculations based on anthropometric data could be used in order to estimate body fat and thus replace the present method It was possible from body weight and subscapular skinfolds in males and from body weight thigh and triceps skinfold in females to reach a proportion of explained variance of body fat of 58 per cent and 76 per cent respectively

The higher proportion of explained variance and the higher correlation coefficients in females can be attributed to the higher amount of body fat in this sex It also seems from this analysis that skinfold measurements on the trunk (subscapular skinfold) seem to be relatively more relevant for estimation of body fat in males than in females whereas extremity skinfold measurements (triceps and thigh skinfold) seem to be more relevant in females than in males

In this study the difference between the subjects body weight and a standard ideal weight (16) widespread in Scandinavia and in much use in the clinics

at the estimation of overweight was tested regarding its relation to body fat This ideal weight was based mainly on measurements on young and middle-aged individuals and the age range covered individuals up to 69 years That material was not representative of the total population as it only covered individuals with working capacity and employed in o g different industries As far as we know the present study is the first that concerns a representative sample of a higher age population There was a rather good correlation between body fat and the difference between body weight and the ideal weight Regression equations with body fat as the dependent and body weight and ideal body weight as independent variables were obtained which might be used in practical clinical work

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However comparisons between cross-sectional studies must be interpreted with great caution An apparent change of a variable between two age groups might be

the result of - apart from changes of age per se - also secular changes and selective mortality

This paper deals with a part of a broad epidemiological study comprising anamnestic data about previous occupation living conditions physical activity etc and a detailed survey of present social and medical conditions A detailed analysis of the body composition data in relation to the other parameters must wait until a more thorough penetration and evaluation of this latter data has been performed

Furthermore the question whether e g tolerance of drugs is related to changes in body composition will be the subject of further studies

In the population of 70-year-olds in Gothenburg diseases with serious handicaps were unusual However medical findings associated with disease were common It is of great interest to try to define a group of probands without symptoms and signs of overt disease who roughly could be looked upon as healthy and use this group for comparisons with younger populations where disease is more uncommon A separate comparison of the body composition of these healthy 70-year-olds with younger healthy groups is of course of great interest but must wait until other parts of the extensive material have been penetrated further

The study 70-year-old people in Gothenburg is designed to be a longitudinal prospective study and the probands will be reexamined at the age of 75

REFERENCES

1 Allen T H Andersson E C & Langham W H : Total body potassium and gross body composition in relation to age J Gerontol 15 348 1960
2 Arvidsson B Sköldborn H & Isaksson B : Clinical application of a high-sensitivity whole-body counter Proceedings from the 3rd International Conference on Medical Physics including Medical Engineering Chalmers University of Technology Göteborg Sweden p 41 2 Göteborg 1972
3 Arvidsson Lenner R Bengtsson C Carlgren G Isaksson B Lundgren B F Petersson I & Tibblin E : The study of women in Gothenburg 1968-1969 Intake of energy and nutrients in women of five different age groups Acta med scand In print 1977
4 Bengtsson C Blohmé G Hallberg L Hällström T Isaksson B Korsan-Bengtsen K Rybo G Tibblin E Tibblin G & Westerberg H : The study of women in Gothenburg 1968-1969 - A population study Acta med scand 193:311 1973
5 Berg K & Isaksson B Body composition and nutrition of school children with cerebral palsy Acta paed scand Suppl 204:41 1970
6 Bergström J : Muscle electrolytes in man Determined by neutron activation analysis on needle biopsy specimens A study on normal subjects kidney patients and patients with chronic diarrhoea Scand J clin Lab Invest Suppl 68 1962
7 Bergström J Personal communication 1976
8 Burmeister W & Bingert A Die quantitativen Veränderungen der menschlichen Zellmasse zwischen dem 8 und 90 Lebensjahr Klin Wochenschr 45 409 1967
9 Durnin J V G A & Womersley J Body fat assessed from total body density and its estimation from skinfold thickness measurements on 481 men and women aged from 16 to 72 years Brit J Nutr 32: 77 1974
10 Edwards D A W Hammond W H Healy M J R Tanner J M & Whitehouse R H Design and accuracy of calipers for measuring subcutaneous tissue thickness Brit J Nutr 9:133 1955
11 Forbes G B & Reina J C Adult lean body mass declines with age some longitudinal observations Metabolism 19 653 1970
12 Holliday M A Segar W E Lukenbill A Valencia R M & Durell A M : Variations in muscle electrolyte composition due to sampling and to aging Proc Soc exp Biol (N Y) 95:786 1957
13 Hume R & Weyers E Relationship between total body water and surface area in normal and obese subjects J clin Path 24 234 1971

14 Kennedy G C Flear C T G & Parker R A Renal disease and secondary potassium depletion in ageing rats Quart J exp Physiol 45:82 1960
15 Kjellberg J & Reizenstein P : Effect of starvation on body composition in obesity Acta med scand 188:171 1970
16 Lindberg W Natvig H Rygh A & Svendsen K Høyde- og vektundersøkelser hos voksne menn og kvinner Forslag til nye norske høyde-vektnormer Tidsskr Norske Laegefor 76:361 1956
17 Lindholm B Metodik vid balansstudier och mätningar av kroppssammansättningen In Metodik vid nutritionsundersökningar på homo (ed B Isaksson) p 41 Studentlitteratur Lund 1970
18 Montoye H J Epstein F H & Kjelsberg M O The measurement of body fatness A study in a total community Am J clin Nutr 16 417 1965
19 Moore F D Olesen K H Mc Murrey J D Parker H V Ball M R & Boyden C M : The body cell mass and its supporting environment Saunders Philadelphia-London 1963
20 Novak L P Aging total body potassium fat-free mass and cell mass in males and females between ages 18 and 85 years J Gerontol 27:438 1972
21 Rinder L Roupe S Steen B & Svanborg A 70-year-old people in Gothenburg A population study in an industrialized Swedish city I General presentation of the study Acta med scand 198: 397 1975
22 Seltzer C C Stoudt Jr H W Bell B & Mayer J : Reliability of relative body weight as a criterion of obesity Am J Epid 92:339 1970
23 Shukla K K Ellis K J Dombrowski C S & Cohn S H Physiological variation of total-body potassium in man Am J Physiol 224 271 1973
24 Sköldborn H Arvidsson B & Andersson M : A new whole body monitoring laboratory Acta radiol Suppl 313:233 1972
25 Steen B Bengtsson C Bruce Å Isaksson B & Tibblin G : Kroppssammansättningen hos män och kvinnor i olika åldrar i Göteborg - resultat från tre populationsstudier In: Nordisk Gerontologi Förhandlingar från Andra Nordiska Kongressen i Gerontologi i Göteborg 4-7 maj 1975 (ed B Steen A Svanborg) p 213 Astra Södertälje 1976
26 Steen B Isaksson B & Svanborg A : Intake of energy and nutrients and meal habits in 70-year-old males and females in Gothenburg Sweden A population study Acta med scand Suppl 611:39 1977
27 Tibblin G : High blood pressure in men aged 50 - A population study of men born in 1913 Acta med scand Suppl 470 1967
28 Valentin N & Olesen K H : Measurement of muscle tissue water and electrolytes Scand J clin Lab Invest 32 155 1973

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The Interactions of SMOKING, ENVIRONMENT AND HEREDITY and Their Implications for Disease Etiology

A Report of Epidemiological Studies on the Swedish Twin Registries

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CONTENTS

1 INTRODUCTION

As long ago as the 1 te fifties based on paper by Doll and Hill (1956) Hammond and Horn (1958) Dorn (1958 1959) and others great attention began to be paid to an association between tobacco smoking and disease above all lung cancer The epidemiological evidence f causal connection was however questioned by sever l author among whom Fisher (1958) and Berkson (1958) argued that the statistical relationship was not causal but dependent on factors rel ted to the smoking habit as well as to disease This discussion l ter became known as th cancer controversy an expression which was taken from publication by Fisher in 1959 advancing the theory that smoker and nonsmokers are genetically differ ent The propensity to become smoker or at least to tay smoker after having begun should in some way be genetically linked to an increased susceptibility to develop disease During the years this theory has met trong opposition It seems now to be ruled out by a maj rity of researchers in regard to certain respiratory diseases in- cluding lung cancer whil few still question the causality (Burch 1975; Sterling 1975) The genetic theory should howeve deserve serious ttention in regard to other diseases that have been shown to be mor prevalent among smokers than among nonsmokers - such as coronary heart disease an entity that in regard to numbers i far more important cause f death than is lung cancer

The opinion in regard to smoking and health has been reflected in periodi cally appearing documents from the US Publi Health Service such as the Surgeon Gene al Reports (1964-1975) in reports from the Royal College of Physi ians of London (1962 1971) and recently in report from the World Health Organization (1975) The last mentioned report states that smoking is an important causative factor in lung cance chroni bron- chiti and emphysema ischemi heart disease and obstructive peripheral vascular disease No recognition was given to the possibility that some f the apparent ffects could be due to confounding i environmentally or genetically determined associations between smoking and the poten- tially hazardous habitual factors such as alcohol or drug abuse

Whether compl tely environmentally determined or to some extent influenced by genetics as well it is obvious that smoking is more common in certain population trata defined by sex age ace urban-rural residence education and occupation There also are great diff rences between different countries Further within individual the smoking habit is associated with drinking and food habits physical and social ctivities etc factors that may involve isk f their own for provoking disease This may lend support to an assumption of smoker personality characterized by an outgoing life-styl and tendency to neglect health affecting factors

It is common knowledge that many disease entities to some extent are influenced by geneti factors This influence does not have to be looked upon as musative t ll but may till play significant part in the late development of the disease There is trong evidence for exampl that longevity is markedly influenced by the geneti code

These considerations necessarily give support to the view that a scientific assessment of the association between smoking and disease experience could with few exceptions not be valid without control for possible intervening and confounding variables among which genetic factors may be of decisive importance To meet this end a model should be developed to control for the influence of environmental covariables and genetic factors - making it to some extent possible to distinguish between the causal and constitutional hypotheses

Against this background the Department of Environmental Hygiene of the Karolinska Institute in 1959 drew up plans for a continuing epidemiological research program based on population studies of twins

A twin registry was compiled in 1959 1961 that covers about 11 000 samesexed twin pairs born 1886-1925 with both partners alive at the time of compilation A series of mailed questionnaires furnished information about smoking and drinking habits a variety of dose-related variables and health parameters Subsamples of the twins have subsequently been clinically examined to meet various specific purposes such as validation of questionnaire data The twins have been followed up to obtain mortality data The program was extended in 1967 when the same type of study was performed in collaboration with the Follow-up Agency of the National Research Council National Academy of Sciences Washington DC This study covered more than 4 000 male twin veteran pairs born 1917-1927 and belonging to the National Research Council (NRC) Twin Registry A further expansion of the twin-program was afforded in 1971-1975 when the Swedish Twin Registry extended its files to include another approximately 13 000 samesexed pairs born in 1926-1958 and alive in 1971

Special methods have been developed to analyze the data one main feature of which is to compare an evaluation of smoking relationships among all twins regarded as a sample of nonrelated individuals with results obtained in groups of smoking discordant twins The methodology as well s the results of these studies have been reported in about 30 publications among which six are doctoral dissertations Data on certain aspects are still not conclusive due to small numbers among other things; even so they do elucidate the smoking and health issue in a perspective that has hitherto been but little recognized It has therefore been considered useful now to publish a comprehensive review of the research program and to present an overall assessment of the results

Though one major aim is to review results reported in previous papers dealing with the registry the present publication does contain a l rge amount of unpublished data especially in the chapter dealing with th smoking related disease panorama The latest report on mortality appeared in 1973 and covered an 11-year follow-up including June 1972 Data from another three years of follow-up have allowed a more detailed analysis of the cumulated mortality and are presented in this report

The major part of the studies referred to in this volume has been carried out at the Department of Environmental Hygiene of the Karolinska Instit te and of the National Swedish Environment Protection Board (up to 1972 th last mentioned Department was a division of the Swedish National Institute of Public Health) The clinical studies as well as other studi s have been carried out in collaboration with the Department of Internal Medicine of the Karolinska Institute at the Serafimer Hospital The studies on

the US twin registry of the US National Research Council were carried out in 1967 when two f the authors (RC and LF) worked as vi iting scientists t the Kettering Laboratory f the Univer ity of Cincinnati

The present compilation has been funded as a Special Project of the Council for Tobacco Research USA Inc report of which was submitted in February 1977 With some revisions it is now published with support from the Swedish Medical Research Council The research work has during the years been carried out with grants from different organizations The formation f the first Swedish twin registry was supported by grants from the Swedish Medical Research Council the Folksam Insurance Company and the Swedish Tobacco Company upon the recommendation of its medical advisory board The clinical studi to great extent have been supported by the National Swedish Association against Heart and Chest Diseases Since 1969 the major funds for the continuous follow-up f the ld Swedish twin egistry have come from the Ameri an Medical Associa tion Education and Research Foundation This foundation together with the National Center for Air Pollution Control of the US Public Health Service also funded the tudies on the US twin registry in 1967 The formation of the new Swedish twin registry 1971 1975 has been supported entirely with funds from the Research Committee f the National Swedish Environment Protection Board. As of 1975 the Council for Tobacco Research USA is funding the Swedish studie into tobacco and health

For technical assistance in the prepar tion of thi report the authors re indebted to Ingrid Lundberg BA Ulla Lorich BA and Margit Dahl quist. Pamela Boston BA has revised the English translation

2 THE TWIN APPROACH

2 1 Theoretical Concepts and Models

2 1 1 The phenomenon of twinning

One-egg twins are nature own contribution to experimentation providing two identical individuals i two human beings of the same genotype Further these two indi idual have experienced very similar environment before birth as they will during many years in their childhood The phenomenon of identical twinning is explained by an accidental and immediate partitioning f the fertilized eggcell This is not too uncommon occurrence but its exact te is unknown as spontaneous and ea ly abortions f equently ensue The birth-rate of one-egg (lso called identi al monozygoti) twin pairs is fairly constant and does not diffe considerably between different population groups Among Caucasians the te pe thousand full term prégnancies has been estimated at 3 7 (Morton Chung and Mi 1967) There is no conclusive evidence that the phenomenon f monozygoti twinning is related to hereditary factors or ther special characteristics of the parents (Bulmer 1960)

Another kind of twin pair develops from two concurrently f rtilized eggcells; they are called two-egg twins fraternal or dizygotic From geneti point f view the partners f dizygoti set are no mor imi lar than ordinary iblings but they do experience much more similar environment both before and after birth than do ordinary siblings The tatistical expectation as to the number of genes they have in common is 0 5 the same as ordinary iblings have

Dizygoti twins may be f the same sex or of opposite sex based on andom occurrence the expected number of samesexed pairs is the same as the umber f opposite-sexed pairs Among the same-sexed pairs the fraction f males corresponds to the sex-ratio which in Sweden is roughly 1 04

The te of dizygoti twinning differ considerably between different populations Whil the te f dizygotic twinning in the Caucasian race i on an average 6 6 per thousand pregnancies it is much higher f exampl in Nige ia with ate f about 40 per thousand whil it is only about 2 3 in Japan (Morton Chung and Mi 1967) The explanation is not only aci l It is known that the chance for dizygotic twinning increases with the age f the mothe and independent of age also with the umbe of her pregnancies factors that are associated with the social and thnic environment In observations from England and Wales the total twinning te ranged from 8-16 pe thousand the lower number representing first pregnanci and the highe representing women who already had given birth to 5 more children The chance of having twins as esult of the first pregnancy is little more than 50 percent higher for women ove 35 than below that age (Deene and Keene 1972) The rates refer to total twinning but the differences depend on increases of dizygoti pairs

Multipl births ar not confined to twins The occurrence f triplets is very are howeve having rate of about the square of the twinning

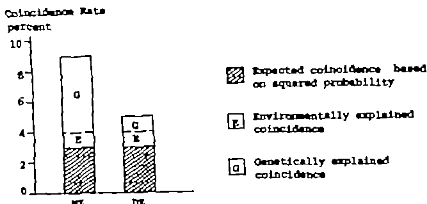


Figure 2 1 Model for Interp etation of the Coincidence Rate (explanation see text)

The total height of the bars represent the observed coincidence rate and the shaded parts the expected coincidence rate It appear that the observed coincidence te i about twice as high in the monozygoti group compared to the dizygotic Even for the dizygotic group however the observed coincidence rate is higher than expected Conventionally the difference (E+G) between observed and expected coincidence tes measures in both zygosity groups the influence of environmental and genetic factors shared by the two partner Assuming that the strength f the environmental influence is the same in the monozygoti and dizygotic pairs the difference in G between the total heights of the two bars i due to the genotypi identity of the monozygotes It has repeatedly been pointed out however that this assumption may not be completely valid There are indications showing that the members in monozygoti pairs tend to share mor similar environment than do the members in dizygotic pairs (Östlyngen 1949; Smith 1965; Cavalli Sforza and Bodmer 1971; Vandenberg 1976) It can be shown for instance that habitual factors like smoking and drinking ar more imilar within the monozygotic pairs than within the dizygotic ones (Friberg t al 1959; Kaij 1960; Shi lds 1962; Partanen Bruun and Markkanen 1966; Jonsson and Nilsson 1968) Thi may in itself be an indication of geneti inheritance in regard to these traits but it may just as well sol ly indicate an environmental ffect i environmental pressure toward conformity Whatever the cause this higher degree of imilarity has a biasing ffect when the hereditary influence on certain disease endpoint i evaluated provided the disease is etiologically or genetically related to the habitual factor in question

In regard to quantitative traits i traits that can be assessed by rank order interval or rati scales concordance can be assessed in terms f intrapai variances or correlations Here it is assumed that the va iance within monozygoti pairs part from rror variance is sol ly due to environmental influence whil the variance within dizygotic pairs is caused by environmental as well as genetic influence Sever l different kinds of heritability indices have been developed Some criticism has been voiced in regard to the validity of these mea-

rate; quadruplets and quintuplets are very seldom observed The recent use of hormone-based drugs to enhance fertility by an increased ovarial production has given rise to an increase in the rate of multiple births (Cavalli-Sforza and Bodmer 1971) This is not assumed to affect the rate of monozygotic multiple births however

Starting with Galton in the nineteenth century the phenomenon of twinning has long been utilized in science for various reasons The so-called classical twin-method aims at distinguishing between the influence of heredity and environment The co-twin control method takes advantage of the genetic identity in experimental or semi-experimental designs Both methods will be presented below

2 1 2 The classical twin-method

The basic assumption for the classical twin-method is that the two members of a monozygotic twin pair share their environment to the same extent as do the two members of a dizygotic twin-pair If this were the case any greater resemblance between the two monozygotes as compared to the two dizygotes would be due to the genotypic identity This concept apparently needs to be bolstered by a definition of resemblance

One measure of resemblance used for qualitative or quantal traits like disease and no disease is the concordance rate This rate can be measured in different ways of which the so-called proband concordance is the most general and defined as the proportion of affected individuals among co-twins of previously defined index cases (Allen Harvald and Shields 1967) This definition has been most used in the literature the main reason being that it estimates the concordance rate in the population which at the same time is equal to the conditional probability that one twin is affected given that the co-twin is affected

In many studies on twin samples obtained from hospitals or outpatient clinics the investigator will encounter positive cases and h may get in touch with the co-twin through the positive partner This gives him a sample of twin pairs where at least one member in th pair is positive The likelihood of finding concordant pairs in this procedure is greater than finding discordant pairs Appropriate methods of coping with this problem usually based on the proband rate have been worked out Under some conditions a suitable way of expressing resemblance in such cases is the so-called pairwise concordance defined as the proportion of pairs where both are affected in relation to all pairs where at least one is affected The influence of incomplete ascertainment on concordance rates has been the subject of several publications (Hrubec 1973; Smith 1974; Hrubec and Allen 1975)

In survey studies based on twin registries compiled on a popul tion basis the question of ascertainment is different Depending on the efficiency of the compilation procedure such registries may only be mo e or less complete but the completen ss may only to an insignificant degree depend on the traits under study In such studies the concordance may be measured as a coincidence rate defined s the ratio of all pairs where both members are positive over all pairs including the negative ones This rate has been named the coincidence rate (WHO meeting of investigators on methodology of twin studies 1966) It is a traight forward procedure to calculate th expected coincidence rate which is the square of the prevalence rate for a certain tr it among all individuals in the twin series The findings may be illustrated as in figure 2 1

2 2 The Rationale of the Twin Method in Epidemiology

2 2 1 The basic assumption

In gene al tudies f dose and response cannot be truly valid if they are not performed in "before-after" design or in case-control experiments where cases and controls are chosen randomly Experimentation has been widely used in medicine and a great vari ty of methods has been developed (see g Cochran and Cox 1960) The view that only experiments are alid although theoretically perfect defendabl has to be considerably modified in epidemiology where with few exceptions experimentation is impossibl To a great extent the epidemiologist has to base his results on the basis of ex post facto experiments the rationale of which is to classify randomly selected individuals into groups of unexposed and already exposed individuals (see g McMahon Pugh and Ipsen 1960) If exposure is true random event and not correlated to other risk factors the two groups under study are just as comparabl as would be two groups selected on the basis of randomization procedures In egard to most exposure factors the concept f random dose induction i questionabl particularly for self induced exposures lik smoking drinking and drug consumption It has been well documented that individual so xposed show characteristics that the nonexposed do not (cf section 6) Acquisitions f these habits cannot be regarded random events It i also ften true that the habits go together" and are thus not mutually independent If the influence of such correlated exposures cannot be controlled it has to be nullified by "restriction which means that all individuals in both groups must be selected as g nondrinkers or nonusers of drugs Such restriction seems to be easy enough to perform in regard to few well defined variables but becomes xtremely complex if the dose facto is also associated with certain occupations urban-rural residence differences physical inactivity and other life-styl variables and possibly also psycho-social factors

In principle multivari t design could be a solution to the problem In practice howeve several questionmarks will remain There may exist correl tes to the exposure factor which re not known and thus cannot be controlled Some influencing factors may be known or assumed but cannot be measured which is the case with most genetic factors

The importance of contr lling for genetic factors depends on how likely it is that such factor play a part in the development of the disease under study and t the same time are associ ted with the exposure factor and its correl te In regard to smoking for exampl the habit can be assumed to be part f complex constitutionally" induced life-style that expresses itself not only in smoking but lso in drinking drug consumption nightlife physical inactivity and other habits that can be regarded potentially unhealthy and disease-precipitating It can further be assumed that this constitutional type in itself and independently f the exposure facto has a genetic predisposition for developing certain diseases This last assumption has been named the constitutional hypothesis opposed to the causal hypothesis which implies that the exposure factor itself is causally related to the disease

surements mainly with a view to the questionable similarity in environ ment concordance between monozygotic and dizygotic pairs A thorough discussion of quantitative concordance measures is given by Cavalli Sforza and Bodmer 1971 and Smith 1974

2 1 3 The co-twin control method

The co-twin control method is essentially experimental i e focusing on the testing of hypotheses about cause and effect under matching conditions The validity of any true experiment is due to the fact that the two groups of individuals to be compared the probands and the controls if randomly selected have the same expected mean for any variable to be studied This makes the two groups ideally comparable but does not decrease the variance within each group A way to separate out this interindividual variation is to constitute pairs within which as many variables as possible have the same value or are controlled In all matching the degree of control is dependent on the magnitude of the intrapair correlation i e to what extent the matching variables really have the same values within the pairs In monozygotic pairs this correlation is unity in regard to genetic factors but many also be assumed to be high in regard to many environmental factors

The co-twin control method has been widely used in the fields of psychology and education for example in regard to the learning potential of different teaching methods (see e g Gesell 1942; Husén 1953) It has also been used in testing drugs or different treatments in cases where the effect is assumed to be related to individual characteristics with high interindividual variance (Glass 1954; Cerasi and Luft 1967; Alexanderson Evans and Sjöqvist 1969) The method in its true experimental form has found but little use in epidemiology A semi-experimental mod l of certain potential in epidemiology is to compare differences in response between ex post facto exposed and unexposed partners in series of monozygotic and dizygotic twins This is the rationale of the twin method in epidemiology and it will be described in detail in the following sections

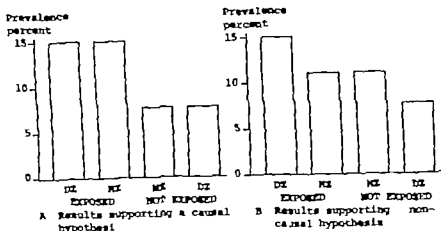


Figure 2 2 The B-series model (explaination see text)

If the trait had been a disease entity figure A would have supported causal and figure B noncausal hypothesis It should be pointed out that the lik lihood of finding complete verification of eithe hypothe- i is small for several reasons For many exposur factors it may be asonabl to assume that both constitution and the factor each pe se or i inte action may have true ffect on the disease or mortality entity The problem is quantitative rather than a qualitative one

If the trait under tudy had been competing exposure factor say for example lcohol drinking in smoking discordant pairs an outcome accor ding to A would have demonstr ted no control f drinking whatsoever in the comparison within the monozygotes whil the outcome according to B would hav demonstrated compl te control

The degree of control is of fundamental importance in connection with verification f the causal hypothesis in regard to th exposure factor unde study but i of much less importance in connection with possible verifi tion f the constitutional hypothesi If neither alcohol drink ing nor drug consumption is controlled to any extent the discriminating model has lost an important part of its power It may still be possibl to combine the model with restriction or with multivariate analysis Even i the analysis shows reasonabl control of all measured variables there i still possibility that the apparent verification of the ausal hypothesi is false because f an unknown and unevaluated compet ing environmental isk factor correlated to the exposure unde study

The noncausal outcome may also be biased This would not be due to incompl t control The major criticism concerns whethe the degree of discordance in the exposure factor between the exposed and nonexposed twi partner in the monozygoti pair i the same as between the exposed and nonexposed partners in the dizygoti pair (cf section 4 6 2)

An outcome in accordance with figure 2 2 B would show that nonsmokers in smoking discordant monozygoti pairs have higher prevalence f the

As genetic factors are completely controlled in monozygotic twin pairs a twin approach may help in discriminating between these two opposing hypotheses provided that enough numbers of pairs discordant for the exposure can be found Genetic control is not sufficient however if it does not at the same time afford a control of environmental etiologic factors such as the above mentioned habits Such control cannot be expected to be complete but may be considerable in view of the importance of early childhood for the development of physical and social traits

2 2 2 The discriminating model

The general approaches to the analysis of empirical twin data are manifold The following paragraphs will describe and explain the analyses employed in the present report

First the series of twins is regarded as a number of unrelated individuals distributed in regard to the exposure variable into several categories which if possible are quantitatively assessed This analysis in the model is named A series analysis The statistical evaluation has taken into consideration possible age and sex differences but only to a very limited extent other measurable exposure correlates The A analysis is performed as a confirmation that generally known statistical associations between the exposure factors and disease also exist in the sample studied The outcome can also be taken as a validation of the measurement methods for both exposure and response variables as a negative finding could be due to insensitive methods If such insensitivity can be regarded as unlikely on the basis of other evidence further analysis could still be expected to yield meaningful information if the expected relation between dose and response is hidden or confounded by dose-factors other than the one under study

The second approach to the analysis is based on monozygotic and dizygotic twin pairs discordant in regard to the exposure variable This analysis in the model is named B-series analysis The rationale of the method is to compare the outcome between exposed and nonexposed twins in both the monozygotic and the dizygotic series in regard to the effect variable assuming that the competing influence of confounding variables is decreased especially in the monozygotic series The decrease of the influence of such confounding variables say drinking behavior is named control and implies an enhanced group comparability The control may be due to the influence of gen tic or environmental factors or both The results can be displayed as in figure 2 2 A and B

In each chart (A and B) the exposed individuals from the pairs in the B series analysis are on the left side of the graph and the nonexposed on the right side The results from the monozygotic twins are displ yed in the two middle bars and those from the dizygotic twins in the two outside bars Figures A and B illustrate two possible extreme outcomes of the analysis In A there is a notable difference between the exposed and the nonexposed twins in both zygosity series Whatever genetic or environmental control has been achieved in using monozygotic twins the relationship between the trait under study and the exposure factor i unchanged Figure B displays the same differences as in figure A between exposed and nonexposed dizygotes There i however no diff re ce between the exposed and nonexposed monozygotic twins Whatever genetic or environmental control has occurred there is no statistical associ tion between the exposure factor and the trait under study in the monozygotic se ies

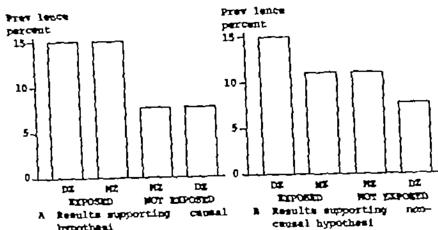


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The nonc usal outcome may lso be biased This would not be due to incomplete control The major criti ism concerns whether the degree of discordance i the exposure factor between the exposed and nonexposed twin partner in the monozygoti pair i the same as between the exposed and nonexposed partners in the dizygotic pair (cf section 4 6 2)

An outcome in accordance with figure 2 B would show that nonsmokers in smoking discordant monozygoti pair have higher prev lence of the

trait in question than do nonsmokers in dizygotic pairs This is reason able if one assumes that constitutional factors are of importance for the development of smoking as well as for the trait under study and it would be true even if some difference were found between the smokers and nonsmokers in the smoking discordant monozygotic pairs One can then also postulate that nonsmokers in general - in the twin series consist ing for the most part of concordant nonsmokers - would have still lower prevalence rates as those with a possible smoking constitution would be rare and would influence the prevalence rate to a much lesser extent A model has been developed in order to elucidate empirically whether or not such prevalence rate differences exist between different groups of nonsmokers

Within each zygosity group all nonsmoking individuals can be regarded as a finite population of nonsmokers As any parameter e g the prevalence rate of excessive alcohol drinking is known within sex and age groups in this finite population it is possible to calculate an expected mean and variance for any randomly chosen sample of a certain size and with a given sex and age distribution If a sample is not randomly chosen but selected in regard to a certain single criterion that is assumed to be unrelated to the item under study the sample mean under this assumption will be an unbiased estimate of the population parameter and subj ct to random variation only Consequently a significant difference between the sample mean and the sex and age standardized expected value would require the rejection of the hypothesis that the selection criterion and the trait under study are unrelated

This reasoning leads to the following mode of analysis Monozygotic and dizygotic twins were treated separately throughout All nonsmoking twins in each zygosity group were assumed to constitute a nonsmoking popula tion Prevalences for each variable were calculated within sex and five-year age groups Among these nonsmokers several samples were drawn on the basis of the smoking status of the co-twins In this way one sample was formed by the nonsmoking partners of present cigarette smokers another sample by the partners of all present smokers and a third group was constituted by the partners of former smoker A fourth group was formed by the nonsmokers who had a nonsmoking partner i e one twin was randomly selected from all nonsmoking concordant pairs On th basi of the sex and age structure within these samples and the prevalence rates in the population expected values were calculated The diff rences between the observed and the expected values were then statistically evaluated The analysis has been named NET-analysis in the following as it is based on Non Exposed Twins

3 TWIN REGISTRIES AND TWIN STUDIES

3 1 Twin Registries in Epidemiology

3 1 1 Availability of twins

As tated above in most western countries about two percent of all individuals re born members f twin pair If survival time were the same for twins as for ingl tons - which is not altogether true the Swedish population should comprise 160 000 twins and the US popu-l tion more than 4 million The twin approach in epidemiology equire in most cases however that the twin pairs should be unbroken by death t the start of the investigation Thi decreases substantially the target population and when other selection criteri have to be met like those f including only samesexed twins or twins with discordant environmental exposure the target groups become quite small

Most western countri make separate tabulations for twins in thei vital statistics on births To our knowledge however the fact of being born a twin is seldom carried further in population registries Special methods have to be developed f compiling twin registry

Many linical and genetical tudies on twins have been performed on samples the selection f which i closely related to th trait under study For exampl in studies of the inheritance f diabete mellitus each person dmitted to hospitals o outpatient linics operating within certain research rea i questioned as to whethe or not he belongs to twin pai If he does the twin partner is located through the disease bearing twin This compilation procedure is not valid in connection with much epidemi logical research where the main de ign ha to be f the prospective type It i ther fore necessary to define th target str tum ithin the population and to arrive t compl te ascertainment of all twin individuals belonging to that str tum Three procedures may be considered

The most d rect procedure is to ask each individual within the stratum whether he i twin or not Assuming total and true response to this question the sampl has to be regarded as completely *ascertained* Such screening could take place in connection with popul tion census based on individual eporting It i obvious however that the procedure will involve questioning 50 times as many individuals as will be utilized for the tudy Anothe method is to use individual birth records as start ing point to identify the twin births by name or number and to try to locate them in the general population. This seems to be an ideal proce-dure provided that each individual were given unique number t birth which he kept throughout his lif and further that the registry of the current population contained this number and that the investigator had access t it This is presently the case in Sweden but the procedure has been oper ting for only little more than 10 years and thus it is not helpful i locating twins born before that date

Neither of these twin procedures gives any information on what has happended to the twins that were not found The third procedure which is rather complicated and can be used in very few countries is to follow up the individual from the parish or registration area in which he was born by tracing his movements from place to place until he finally is found either deceased or living at a certain address This process will also furnish data about the migration pattern - even emigration to a certain point - and gives statistics in regard to mortality These two last mentioned procedures were combined in the compilation of the Swedish twin registries

Other procedures of unknown merit - but probably relatively unreliable in regard to completeness - are to advertize for twin pairs in news papers magazines television etc

3 1 2 The WHO survey

As has appeared from the above section the availability of twins is quite restricted in small countries Because of the numerous variables that have to be used as group defining criteria epidemiological analysis requires a large number of individuals One way to enhance the possibilities of a meaningful analysis would be to seek cooperation with other countries where twin registries are under operation To this end the World Health Organization in 1965 (WHO meeting of investigator 1966) made a survey by sending a mailed questionnaire to researchers who were known to the Organization to be involved in twin studies The result of the survey has been summarized as follows

Out of 39 reported twin series covering in all about 60 different ongoing or planned research projects about two thirds are of the selected type i e obtained from hospitals clinics school etc The remaining registries cover whole populations or well defined parts of a population; about one third of these however contain data obtained from birth records only The twin se ies vary in size from 40 to 50 pairs to more than 20 000; the smaller series mostly consi t of case studies and the larger complete populations Twin s ries of the non lected type and large enough for use in epidemiological investigations are av ilable mainly in the USA and in the Scandinavian countries Some of th se include current addresses of twins oth rs do not at prese t but comprise a large number of twins and must be looked upon as very impo tant sources for epidemiological work

This was in 1965 Large scale epidemiological studies on twins out ide Scandinavia and the USA have not hitherto been ported but some re under way in Finland and others might be expected from othe count during coming decades

3 1 3 Operating registries

The first fairly large scale epidemiological investigation of twi concerning genetics and the epidemiology of chroni dise s i rel ti n to smoking were publi hed by Danish resea ch r (H ug et al 1968; Harv ld and Haugo 1970; Haug Harvald and Reid 1970) Dat we e b ed on a regi try that wa et up in 1954 comprising about 7 000 s t of twin of which 2 500 were of diff rent s x

The Swedish twin registry began its oper tion in 1959 and the first reports began to appear in the early 60 The egistry covers about 11 000 same-sexed twin pairs in the cohorts 1886-1925 It covers both males and female and has mainly been used for tudies concerning smok ing morbidity and mortality Some clini al studies on subsamples have specifically focused on respiratory and coronary disease

The Swedi h twin registry was extended in 1971 to cover another 15 000 same-sexed twin pairs in the cohorts 1926-1958 The studies on thi extension f the registry in addition to the above mentioned smoking rel ted tudies will be used for investigating the impact of the n-vironment in general

In the US twin egistry was set up from birth certificates and ecords of the Veterans Administration in the beginning f the 60 and has ince the been maintained by the National Academy of Sciences (Jablon t al 1967) An epidemiologi al tudy using mailed questionnaire was carried out in 1967 covering about 4 400 mal twin pairs This tudy in collaboration ith the Department f Environmental Hygiene also focused on medical problems connected with tobacco smoking The registry has ince been used for other tudies

The Swedish and US twin tudies will be described in detail in the f llowing sections

3 1 4 Aspects for future registries

As mentioned abov int rnational cooper tion seems to be important and necessary to furnish enough material for studying the effect of environmental exposures on twin pairs discordant for such exposures In orde to find support f these endeavors and to discus problems of coordina tion and standardis tion international meetings have been convened upon three occasions

The first meeting organized by the World Health Organization and mentioned above (WHO meeting f investigator 1966) con idered methodological problems f twin tudies in regard to determination of zygosity sampling techniques organization and maintenance of twin registri and analysis and presentation f results The meeting greed that coope ti ff rts should be made in orde to assist comparison between exist ing and futur twin tudies The group st essed the need f r samples of considerabl ize in order to obtain discordant twins f r comparative analyses f enviromental ffects in chronic conditions

The second meeting w set up unde the sponsorship of the Department of Environmental Hygiene f the Karolinska Institute and was held in Puerto Rico in December 1969 (Twin Registries in the Study of Chroni Disease 1971) Apart from thorough evaluation f results hitherto obtained from twin tudies on smoking and health the main goal of the meeting as to stablish tandardized procedures for survey investigations as well tandardized measuring techniques possibl to apply in epidemiologi l fi ldwo k It was the consensus of the convened group that twin tudies should be tended in va iety f populations in different geog phi l and ethni settings It was further stressed that to interpret the l of smoking and disease it will be essential to col lect data on other living patterns and environmental f ctors as well as personality type behavior and the more commonly recognized risk factors

After the meeting in Puerto Rico and with financial support from the Council for Tobacco Research site visits were made at various research centers in order to stimulate the interest in twin research and to seek cooperation for performing extensive studies on environment and health using twin samples As a result of these efforts a number of researchers convened at a meeting at Miami Beach in 1972 The meeting strongly emphasized the need for standardized methods and that a common questionnaire should be worked out The interest in cooperation was great but the possibilities of effectively establishing registries in several places were not good enough to recommend an undertaking at that time However the Institute of Hygiene in Helsinki Finland proved to have excellent possibilities of compiling a Finnish twin registry to cover 10 000 15 000 pairs The registry is now on its way and it may be followed by several others A twin research program has also been initiated at the Kaiser Foundation the Permanente Medical Group California USA which will cover close to 8 000 pairs

3 2 The Swedish and US Twin Studies

3 2 1 Target populations

The Swedish twin studies have been performed on two targ t populations diff ring only by year f birth and year of compilation The first target population was defined as male and femal samesexed twin pair born 1886-1925 and still living within the country as unbroken pairs in 1961 i the year of compilation The second target population was defined in the same way but comprised pairs born in 1926-1967 and unbroken t the time f ocmpilation in 1973 Emigrants from or immi g ants to Sweden are not covered by the definition

The target population in the US study was defined as mal twin pairs born in 1917 1927 where both members had served in the US Armed Forces as ascertained through the Veterans Administration All except 9 states in the continental US were covered

The target populations in the Swedish and the US studies differ conside ably Whil the Swedish target population in comparison with the total Swedish popul tion is biased only in regard to the requirement of conco dant survival up to the day of compilation the US study is restricted to special population group The requirements for registration with Veterans Administration imply that both members of the pair were physic-ally fit t the time of the induction into the Army

3 2 2 Compilation procedures

The first step in the compilation of the olde part of the Swedish registry wa scanning f all birth registries to find birth records giving date and place of birth family name and the first names f the twins parents This procedur involved scanning of about 5 million entries and yielded total number of same-sexed pairs amounting to about 41 000 liveborn pairs number that devi ted less than 0 1 pe cent from the fficial statistics on twin births during the period

The second tep in the procedure was to rrange the inital file by county and birth t mail lists to each of the 25 counties in Sweden and to ask the egistra ffice to give information about twins born in the ounty In thi way ll twins till living in their county of birth wer loc ted t thi stage the current addresses of one or both part ne i about 16 000 pairs were obtained A twin pair wa considered located as soon the addres f one partner was obtained As expected large number of pairs subsequently had to be discarded because the non-located partne turned out to be dead

F llowing this second step in the compilation procedur about 60 percent f the original number of twin pair remained to be traced Of thi remainder it could be expected that many of the indi iduals had died in thei birth parish Thus the remainder of the fil was arranged by birth pa ish and li ts wer distributed to ll 2 000 or so parishes asking the pa i h office to return information on the twin pairs on the list tating whethe they had died in the parish or had moved to another pa i h Again in cases f death the pair was discarded from the fil In ases f migr tion to another parish the new parish was asked for information about death or migration and so on In thi way the remainder

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of untraced twins gradually became smaller At a stage when less than 15 percent remained untraced it was decided to stop these procedures New lists covering the total remainder were then sent to all 25 counties After this step in the procedure there was still a remainder numbering slightly under 2 000 pairs Once again the parish officers had to be contacted Finally about 1 000 of the original 41 000 pairs had to be discarded as untraceable

The compilation was not yet complete The located twin partners in all pairs from which only one address had been obtained had to be contacted The number of such cases was around 14 000 About 8 000 of these twins reported that their co-twin was dead about 5 000 reported the address of the co-twin and about 1 000 failed to return the questionnaire Finally a total number of 12 889 pairs had been located with known addresses of both partners It could be calculated that this number of pairs covered at least 91 percent and probably more than 95 percent of the actual target population d fined above

It should be mentioned that this compilation procedure was complicated expensive and time-consuming It was performed during a time when the Swedish population registry was not yet computerized and only few of the individuals had a unique birth number It is not possible to tell how significantly the twin eries obtained deviates from th actual target population Most probably a large number of the missing individuals were dead or had emigrated In many cases however they may have been institutionalized or may belong to the category of "missing persons who for unknown but probably social reasons escaped the registration by the authorities

The second part of the Swedish twin registry s t up in the beginning of the 70 was compiled at a time when the Swedish population registry was fully computerized The first step of the compilation procedure namely the screening of the birth records had to be the same however since the data record on tape did not contain information about twins Opposite-sexed pairs were also included in the compilation base of the study According to official statistics 44 636 pairs were recorded as liveborn in complete pairs This initial file could then be computer matched to the registry of the total living population The procedure was not quite straightforward though as a large number of th twins born before 1950 did not have a unique birth number The difficulties were ov rcome by using other characteristics like birth county initial of family and given names etc The resulting fin l number of twin pair available for study amounted to 40 991 pairs

The efficiency of the compilation procedure used for the new twin reg try was better than that for the old one in regard to cost and time elements It seems also to have been efficient in regard to yield Among those not located according to the procedure described 50 individual were selected and processed according to the same procedure as had been followed for the old registry 44 were found to be dead 3 had emigrated and 3 were found to be living within the county (Hedlund et al 1977) Although this sample is small the yield grees f i ly well with the yield of 90-95 percent of th pairs estimated as loc ted by the compila tion procedure for the old registry

The US registry was also established from birth certificates The targ t population w s all white male multiple births in the years 1917 1927 in all except 9 states of the continental US (Jablon et al 1967) Of

Table 3 1 Number of Compl te Pairs in the 1961 Questionnair Study on the Older Cohorts of Swedish Twins by Sex Age and Zygosity

	DIZYGOTES		MONOZYGOTES	
Year f Birth	Males	Females	Males	Females
1886-1895	218	388	190	212
1896-1905	576	810	330	405
1906-1915	1009	1228	526	646
1916 1925	1181	1442	603	744
Total	2984	3868	1649	2007

the pproximately 54 000 pair identified in this way about 16 000 pairs were found in the Master Index file of the V terans Administra tion indicating that both members of these pairs had undergone military service Service personnel and medical records were abstracted for the l tter group to determine medical histories during the service period and get information on physical characteristics that are helpful in lassifying zygosity Survi al f members of these 16 000 pairs was monitored through record resource of the Veterans Admini tration Pilot evaluation indicated that mortality ascertainment is about 97 percent complete Medical hi tories have been updated through questionnaires and from records f the Veterans Administration for those obtaining medical ca through that organization

3 2 3 The questionnaire surveys

The fir t Swedish questionnaire wa mailed 1961 and was to some extent part f the compil tion procedure it was lso used to obtain the address f the co-twin in pairs where only one twin had been located Furthe the questionnaire asked for information about smoking habits esidential history in very broad terms some sociological background variables such as education and marital tatus and series of questions pertaining to the diagnosis of zygosity Detail on the diagnosis will be given in section 3 3 Out of the total number of 12 889 pairs availabl for study 23 429 individual returned thei questionnaires corresponding to response rate of 91 percent.

Of primary interest however is the number of pairs where both partners have turned thei questionnaires Those figures distributed by sex age and zygosity re given in tabl 3 1 above

The nonresponse rat counted in pairs amounted on an verage to 15 1 pe cent and was by and large the same for all sex and age groups with a possibl tendency to higher nonresponse in the younger groups It appear ed that zygosity could not be determined in 439 pairs or 4 0 percent

A second questionnaire was mailed about year fter the first survey had been completed Thi questionnaire contained medical as well as soci logical information Apart from some questions pertaining to the past history of disease experience and hospitalization the questionnaire focused on present symptoms in regard to espiratory and cardio-

of untraced twins gradually became smaller At a stage when less than 15 percent remained untraced it was decided to stop these procedures New lists covering the total remainder were then sent to all 25 counties After this step in the procedure there was still a remainder numbering slightly under 2 000 pairs Once again the parish officers had to be contacted Finally about 1 000 of the original 41 000 pairs had to be discarded as untraceable

The compilation was not yet complete The located twin partners in all pairs from which only one address had been obtained had to be contacted The number of such cases was around 14 000 About 8 000 of these twins reported that their co-twin was dead about 5 000 reported the address of the co-twin and about 1 000 failed to return the questionnaire Finally a total number of 12 889 pairs had been located with known addresses of both partners It could be calculated that this number of pairs covered at least 91 percent and probably more than 95 percent of the actual target population d fined above

It should be mentioned that this compilation procedure was complicated expensive and time-consuming It was performed during a time when the Swedish population registry was not yet computerized and only few of the individuals had a unique birth number It is not possible to tell how significantly the twin series obtained deviates from the actual target population Most probably a large number of the missing individuals were dead or had emigrated In many cases however they may have been insti tutionalized or may belong to the category of missing persons who for unknown but probably social reasons escaped the registration by the authorities

The second part of the Swedish twin registry set up in the begin ing of the 70 s was compiled at a time when the Swedish population registry was fully computerized The first tep of the compil tion procedure namely the screening of the birth records had to be the same howeve since the data record on tape did not contain information about twins Opposite-sexed pairs were also included in the compilation base of the study According to official statistics 44 636 pairs were recorded as liveborn in complete pairs This initial file could then be computer matched to the registry of the total living population The procedure was not quite straightforward though as a large number of the twins born before 1950 did not have a unique birth number The difficultie were overcome by using other characteristics like birth county initials of family and given name etc The resulting fin l number of twin pairs available for study amounted to 40 991 pairs

The efficiency of the compilation procedure used for th new twin regi try was better than that for the old one in regard to cost and time elements It seems also to have been efficient in regard to yi ld Among those not located according to the procedure described 50 individual were selected and processed according to th same procedure as had bee followed for the old registry 44 were found to be dead 3 had emigrated and 3 were found to be living within the county (Medlund et al 1977) Although this sample is small the yield agree fai ly well with the yield of 90 95 percent of the pairs estimated as located by the compil tion procedure for the old regi try

The US registry was also established from birth certificates The target population was all white male multiple births in the years 1917-1927 [illegible] (Jablon et al 1967) Of

Tabl 3 2 Number of Compl te Pairs in the 1973 Questionnaire Study on the Younger Cohorts of Swedish Twins by Sex Age and Zygosity

Year of Birth	DIZYGOTES Males	Females	MONOZYGOTES Males	Females
1926-1935	823	1063	516	611
1936-1945	1116	1304	718	880
1946-1958	1764	1803	1058	1242
Total	3703	4170	2292	2733

twins in the same fashion as in the Swedish studies Out of mailing to about 21 000 individuals replies were obtained from both partners in 7 372 pairs Thi group was defined as target group for second questionnaire mailing

The second questionnaire contained about the same information as the Swedish 1967/70 questionnaire Most questions were translations of those used i Sweden The intention was to duplicate and to supplement the Swedish tudy Complete replies from both members f the pairs were obtained for 4 379 twin pairs f which 1 876 were monozygoti

Some sults of the questionnaire studies will be reported in later sections The ample ize on which the results are based learly varies depending on what questionnair study furnished the data; base number ill lways be presented in tabul tions

3 2 4 The clinical examinations

During the course of the twin research program five speci l studies have been pe f rmed among which four have utilized subsamples from the twin egistry f linical examinations The fifth special tudy focused on psycho-social problems in connection with coronary heart disease and was based partly on the questionnaire surveys and partly on linical investi g tions on samples from the general population

Results from these five special investigations will appear throughout the present eport Thi section will present an overview of the aim of the different investig tions and detailed account of the construction f the subsamples from the twin egistry or other samples obtained from the gener l population The special investigations will here be presen- ted in chronological rde

The primary object f the linical investigation by Lundman (1966) was t examine the sociation between smoking and coronary heart disease Lung function was lso examined mainly with view to lucidating whether the assoc tion between smoking and lung function would be detected when the constitutional factor were controlled Further Lundman wanted to ev luate whethe any sociation between smoking and coronary heart disease could be diagnosed on the basis f case history and lectrocar diographi examinations; whether the acut lev tion in blood pressur used by nicotine would result in changes in blood pressur over long pe iod; and lastly whethe geneti factor influence the development f coronary he rt disease

vascular disease The sociological variables aimed at comparing differ ent survey groups in regard mainly to socioeconomic factors The twins were asked about marital status number of siblings and children employ ment status and education

This second questionnaire was mailed to all twin pairs in which both partners had returned the first questionnaire i e 10 947 pairs or 21 894 individuals Returns were obtained from 20 083 individuals or 92 percent The series of complete pairs to be used in the epidemiological study amounted totally to 9 319 pairs or 85 percent

It shall be noted that the nonresponse occurring between the first and second questionnaire to some degree was due to death occurring between the two mailings

A third questionnaire study on the older Swedish twin registry was carried out in 1967 This questionnaire aimed at a closer description of the twin-individuals in terms of habitual factors other than smoking It contained questions about drinking habits food habits physical exercise during work and during leisure time and further questions about working conditions such as change of employment and employer overtime and extra work etc Questions about smoking habits as well as symptoms referring to respiratory and cardiovascular disease were repeated with the same phrasing as in the second questionnaire

The questionnaire was mailed to 10 451 living twin pairs Returns from both members of the pairs containing complete information on smoking habits were obtained from only 6 130 pairs constituting 58 7 percent of the total number of pairs eligible for the questionnaire A follow-up on pairs who had not answered the questionnaire in 1967 was performed in 1970 and embraced pairs who were still unbroken at that time The nonresponse rate was partly due to mortality between the two last mentioned points of time

The second or new" part of the twin registry i e pairs born between 1926 and 1967 up to now (1977) has been utilized for one questionnaire study only covering same-sexed pairs born between 1926 and 1958 The questionnaire was quite comprehensive in addition to most items of the 3 questionnaires mailed to the first part of the registry it covered a series of questions pertaining to the individual s adjustment to society in psychological terms and que tions about drug consumption in terms of tranquilizers and sleeping pills etc Data were also compiled in regard to a detailed residential history type of work and working conditions attitudes about the general environment in terms of annoyance reactions caused by factors such as odors dust or noise at the place of work or place of residence

This questionnaire was mailed to 21 147 complete twin pairs The number of complete twin pairs responding to the questionnaires is presented by sex age and zygosity in table 3 2

The twin pairs in the US National Research Council Registry were approached with two questionnaires The first was mailed to 22 000 individuals and contained questions about similarities of the twins as children It also determined the medical history since completion of military service The replies to this questionnaire were used to determine zygosity of the

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Lundman utilized a subsample from the twin registry and the criteria for selection were the following: The twin pairs should be concordant in respect to urban or rural environment and discordant with respect to smoking habits All the monozygotes were selected at random with respect to age and sex whereafter the same number of dizygotes was chosen with corresponding age and sex distribution All pairs were selected as concordantly living in metropolitan area Lundman invited 247 twin pairs fulfilling these criteria of selection to participate in the study Out of these 196 (80 percent) were examined Of these pairs 92 were monozygotic and 104 dizygotic and they ranged in age from 38 to 77

The reasons for nonresponse are extensively discussed by the author who concludes that the nonresponse did not affect the end results to any appreciable extent

In addition to a sociological interview concerning a more detailed description of the subjects smoking habits and a medical interview focusing on respiratory and cardiovascular symptoms a series of objec tive characteristics were measured physical examination including anthropometric measurements such as skinfold thickness skeletal length and breadth muscular power weight and height and blood pressure; laboratory tests including blood and urine tests x-ray of heart and lung lung function tests such as dynamic pirometry and nitrogen wash out delay electrocardiographic examinations during rest and work nd working capacity Further in cooperation with Blomstrand (Blomstrand and Lundman 1966) laboratory examinations were performed in regard to blood contents of cholesterol triglycerides and phospholipids

A study by Liljefors (1970) focused on hereditary and environmental factors in pairs concordant and discordant in regard to coronary heart disease The purpose of his study was to examine the concordance rate for the various manifestations of CHD in MZ and DZ pairs selected from a population of male twin of working age and to tudy in discordant pairs intrinsic factors associated with CHD in luding anthropometric factors blood pressure lipids and uric acid in serum diabetes mellitus and extrinsic factors such as smoking physical activity and psycho-social variables Liljefors used a subsample from the first Swedish twin registry and his criteria for selection were the following The crude selection consisted of twins from the base material who according to the questionnaire in 1967 were considered to have infarction o angina pectoris Such individuals numbered 189 in 170 pairs To red ce the risk of false positives a preliminary ppraisal of the symptoms of angina pecto i repo ted in the questionnaire was made This a a rule was done by telephone but in some cases by personal i terview Out of these 189 persons 70 described symptoms that were not con dered indic t ve of coronary heart disease and another three cases were not ccessible for study which left 116 persons for tudy di tributed over 104 pair Another 13 pairs had to be discarded as the one twin was not abl to be examined

The Myrhed study was published in 1974 and cent red on alcohol consump-tion in relation to factors associ ted with coronary heart disea e He emphasized that in most earlier studie great intere t ha been devoted to the relationship between excessive alcohol consumption and specific somatic response but that he wanted to examin the extent to which moderate long standing alcohol consumption is accompanied by somatic deteriorations and if it gives rise to factors a sociated with IHD

The material for the Hyrbad tudy was selected on the basi f reports on alcohol consumption in the 1967 questionnaire Certain discordance criteri in regard to lcbol consumption were lso maintained A total f 92 mal pairs aged 45-65 years were invited to participate in the tudy 70 complete pairs were examined among whom 14 war monozygotic and 56 dizygotic No femal pairs were included in the study As in the other medical examinations sociological interview focused on alcohol consumption and purported to confirm the data obtained from the questionnaire survey The medical interview concetned respir tory symptoms such as cough and phlegm asthma and dyspnea s well cardiovascular symptoms according to th full questionnaire of the London School of Hygiene and Tropical Medicine The diagnosis myocardial infarction was based on the medical interview s well as on electrocardiographi measurements Some labo tory t sts including serum enzyme indicators of live damage wer made

The study by Floderus (1974) focused on psycho-soci l status in relation to coronary heart disease nd ssociated disorder The purpose of the study was to investigat whether or not f ctors associated with the psycho-social tatus f the individual were rel ted to premature de th and specifically to death by coronary heart disease At the same time the tudy lucidated the associ tion between these psycho-soci l factors and behavior l cha cteristics such as smoking and drinking as well as other previously documented isk factors in the development of coronary heart disease The study employed the 1967 twin questionnaire esults as well as results obtained from studies on other samples from the Swedish popul tion A most specif im of the study was to develop a psychometric scal indicative of psycho-social discord in regard to the dimensions of tability-instability and introversion-extraversion

The special study groups consisted of sampl from the populations of Gothenborg and Boden compri ing 396 men born 1914-1928 In this study group the variables investigated apart from the psycho-social scal developed consisted of smoking physical activity including heart rate overweight cholesterol and triglyceride level blood pressure and diabetes Coronary heart disease was represented by angina pec tori sever chest pain for more than 30 minutes myocardial infarc tion and family hi tory of coronary heart disease

Another subject group consisted f andom sampl of about 1 200 men and women 25 to 45 year of age selected from the Stockholm area and county in the southwest of Sweden. The nonresponse te in this investi gation performed via mailed questionnaire was 19 percent and the group investigated compr sed 975 subjects

I addition to the psychological scal the va iables investig ted comprised factor f isk for the development f coronary heart disease namely smoking lcohol consumption lack of physical activity and overweight Information on use f tranquilizers and sleeping pills was lso obtained and rel ted to psycho-social instability as validity test f the instability classification

The fifth special study was performed by de Faire (1974) and dwelled upon ischemi heart disease in death discordant twins The specifi objectives f the tudy were to evaluate the geneti influence on coronary heart disease through associations between the occurence of coronary heart disease in the surviving co-twin and the cause of de th of

the partner He further studied associations between the risk factor profile in the surviving co-twin and the cause of death of the partner and lastly environmental differences in the death discordant pairs as elucidated from earlier questionnaires

The target population was constituted by pairs from the old twin registry born 1901 and later where one member of the pair died during January 1 1971 through March 15 1973 and the other member at that time was still alive A total of 262 male and female twin pairs below the age of 60 had become death discordant i e one member in a hitherto unbroken pair died during the period All the co-twins to the deceased twins were invited to take part in a medical examination Out of the 262 twins invited 205 agreed to be examined giving a response rate of 78 2

Apart from a sociological questionnaire about smoking and drinking among other things questions were posed in regard to symptoms of coronary heart disease The physical examination comprised blood pressure measurement and anthropometric measurements such as weight height and skinfold thickness Electrocardiographic examinations were performed during rest and for nearly all the subjects during and after an ergometer exercise test Further x-ray examinations were performed as well as laboratory blood investigations in regard to cholesterol triglycerides and uric acid

In summary these special investigations - apart from the Lundman study that also considered respiratory symptoms - have all focused on risk factors for coronary heart disease Smoking has been the main item of investigation in one study while the others have focused on several other risk factors of coronary heart disease

3 3 Zygosity Determination

Zygosity can be determined with a high degree of reliability from evaluations f ser logi l characteristics Anthropometri measurements such as fingerprint ridge counts can lso be used The more measurements arried out on ach twin pair the smaller is the chance that th diagnoses is in rror By considering the prevalence f the specific genetic marker in the population ther exact probabilities can be estimated as to the degree f reliability These measurements howeve require a personal contact with the individual to obtain blood sample or fingerprint To determine zygosity in small samples and fo exact assessment f special pai such methods may be nece sary Howeve on larg sampl such as re needed for epidemiological studies the exactness of seriological method can not be defended in consideration of the exorbitant costs involved In epidemiology futhermore it is not absolutely necessary to avoid every erro f somewhat less precise method

An alternative to the serologi al or anthropometri method for determining zygosity is an assessment of the physical resemblance of the two twin in a pai It has been pointed out that this resemblance can be very triking even in dizygoti pairs since certain proportion of dizygotic pairs have more than half of their genes in common This type f error has to be accepted possibl but nevertheless it has to be regarded as occurring ldom In large cal study the degree of resemblance between the two twins can be assumed to be reliabl enough for zygosity lassification

The resemblance between the two partners f pai can be judged by inspecting photographs taken in their childhood or t later point in time It was deemed sufficient however to sk both partners in twin pai whethe they egard themselves to have been very alike as children Thi has been the approach in both the Swedish and th US twin studies and the equivalent f the expre ion as alike as two pea in pod" wa believed to be significant indic tion of monozygosity (Cade löf t al 1961; Jablon t al 1967)

Two alternative responses to the peas-in-the-pod question were offered in the mailed questionnaire Statements from both member of the same twin pai that as children they were as alike as two peas in a pod" lassified them as monozygoti If both members checked that they were only f family likeness the pair was regarded as dizygotic If the partners is the pair did not agree in thei answer no diagnosis was made

At an early stage in the Swedish twin program mailed questionnaires containing the zygosity items were sent to regional sample of located twins A andom sample f 200 pairs where both members had returned their que tionnaire was selected for serological analysis The selection was independent of replies to specifi questions The serological examinations comprised five independent systems namely A,A,BO MN Rhesus (determined by anti-C anti-D anti E anti-c and anti-e) haptoglobin and for those twins who were concordant in the first four systems the Gm-serum well All determinations were performed in

accordance with the standard procedure at the laboratories in question[1] On the basis of prevalence of these in the general population the median probability of concordant pairs being monozygotic was estimated as 96 percent

The requirement of agreement within the pairs in regard to the question of "being as alike as two peas in a pod or being of family likeness only led to the omission of 14 pairs According to the questionnaire diagnosis 72 pairs could be regarded as monozygotic and 114 pairs as dizygotic Among the first mentioned 72 pairs 71 were also monozygotic according to the serological determination and among the last mentioned 114 pairs 104 were dizygotic according to the objective tests This implies quite a high rate of confirmation which is the most important validity criterion in an epidemiological investigation of the type intended

On the basis of these results the questionnaire method was found to be reliable enough for an epidemiological investigation A similar procedure was followed in the US investigation The results showed by and large the same degree of reliability

In the Swedish special investigation mentioned above the results of th questionnaire diagnoses were futher validated In the Lundman study zygosity checks were made on the selected pairs using the A_1A_2BO and haptoglobin systems for all pairs diagnosed in the registry A more thorough serological examination in which the MN and Rh-systems were also included was made on the pairs who were not diagnosed in the twin registry Further color photographs were taken of most of the subjects included in the study All but two out of 93 pairs diagnosed as monozygotic in the twin registry were so classed by these methods All 98 classed as dizygotic in the twin registry were so classed on the basis of the above method although some of them displayed blood group and photographic similarity It again should be mentioned that the blood grouping procedure in this subsample did not include as many genetic markers as were included in the validity examination in the Swedish twin registry

Myrhed (1974) also made an extensive serological examination on the pairs included in his study All of the 54 pairs initially diagnosed as dizygotic had the same zygosity according to serological examination and 14 of the 16 pairs initially diagnosed as monozygotic proved to have been correctly diagnosed

In summary the classification of zygosity employed in these studies can not be consid red to be far from the true values The most likely bias would be that traumatic events before or after birth would tend to make monozygotic pairs different and thus cause them to categorize themselves as dizygotic Th discriminating power of the twin model would of course hereby be decreased More serious is the possibility of cl ssifying dizygotic pairs as monozygotic Anyhow this error of classification would also tend to decrease the difference in genetic discrimination between the two zygosity groups and thus unfavorably affect the possibilities of an empirical statistical difference

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1) The blood examinations as to A_1A_2BO MN Rhesus and haptoglobin were performed at the Institute for Medical Genetics University of Uppsala under the supervision of L Beckman PhD The Gm-Determination was performed by R Grubb MD The Department of Bacteriology Univer-

4 CONCEPTUAL CONSIDERATIONS AND CLASSIFICATION OF VARIABLES

4 1 The Concept of Dose and Response

Epidemi logy has adopted its own vocabulary and especially in discus sions of dose and espons expressions are used among which risk factors precipitating factors and intervening factor re common but not always lea ly defined

Presented with a disease of unknown ti logy the researcher first tep is almost always etrospective This implies comparing groups composed of people with and without the disease The whol panorama of possibl causes is studied in the hope of finding some factors that are more prevalent among the diseased people as compared to the healthy Although invaluable in epidemiology the retrospecti design does not have power of its own to point out smoking and drinking as causative agents nor even as risk factors Other factor not known not measur able may theoretically be the real cause and an pparent association between smoking drinking and disease may be spurious or caused by high correlation between the real factor and the pparent one

Prospective research gives rise to another ituation A popul tion of healthy individuals may be subdivided in regard to presumed causative agent If subsequently occurring specific morbidity r mortality turns out to be higher in the group where the presumed causative agent is present than in the ther group this agent is defined a isk f ctor" The prospective pproach make it possibl to test hypotheses regarding the relationship between risk factor and disease but based only on such data and without supporting evidence it i still not theoretically possibl to prove causality for the same easons as have been mentioned above in regard to the retrospective design

Risk f ctor can be external or internal Typical examples of external risk factors re habit like smoking and drinking Such factors can be named exposure factors or dose Other external risk factors re occupational exposures to gases and dusts general air poll tion drug consumption inadequ te nutrition physical inactivity heavy work load tc Among internal risk factors for coronary heart disease are obe ity high blood pressure increased serum content f lipids such as choles ter l t (Björck 1975; Keys 1975; Werkö 1976) The internal risk factors annot be egarded as exposure or dose They ar all bi logical conditions that ither may have genetic origin or may in their turn have been caused by external exposur factors A good exampl is in creased serum cholesterol which is influenced by genetic factors but also depends to a large extent on food habits (Osborn et al 1959; Meyer 1962) In this sense increased cholesterol is partly an ffect factor

The concept of intervening or intermediary factors is not easily de fined It can be hypothesized that personality" is an internal risk facto for coronary heart disease Type A and type B behavior are well documented psychological correlate to smoking as well as to coronary heart disease (Friedman and Rosenman 1959) Personality is f course

a very wide concept It has been mentioned in earlier sections for instance that smokers and nonsmokers may represent different personality types The smoker s personality is characterized not only by smoking but by a series of other habits like drinking drug and physical inactivity (cf section 6 2) If this personality independent of the risk factors it involves is causally linked to coronary heart disease the risk factors may play no other part in the etiology complex than simply being signs or symptoms of this personality They may however just as well play an important role of their own in this psychologically determined environment and may then be regarded as precipitating factors

A few words will also be said about feedback mechanisms A risk factor like smoking may cause a certain disease The awareness of the disease may give rise to maladjustment sleeplessness and other psychological conditions which then in the analysis will show up as correlated with smoking The disease itself is in this way intervening in th relationship and there may be no direct causal link between the mentioned psychological conditions and smoking The interpretation of relations of this kind is even more difficult to make in cases where the disease condition is subclinical and has not been recorded as a manifest disease An example is physical inactivity; certainly nobody would question that a patient with anginal troubles would cease in physical activity long before the disease condition is clearly known to himself

Against the background of these considerations an attempt to classify all variables in terms of dose and response is rather futile Arbitrarily the authors of the present report have chosen to name external risk factors of the habitual type as dose variables and symptoms and signs of disease or mortality as medical effect variables Other variables like socio-economic or psychosocial status have been named covariables as they have been used mainly for control No consideration has been given to the fact that they sometimes may play the role of an internal dose factor or of an intermediate effect

4 2 The Concept of Discordance

In section 2 1 2 the concept of concordance was discussed as means of evaluating pos ibl geneti influence It was mentioned that concordance could be measured with regard to both qualitative and quantitative traits Concordance measurement is an instrument of the classical twin method

In the co-twin control method as it i modified for epidemiological evaluation discordance is fundamental concept In focusing for instance on smoking habits the very target for the twin analysis i pairs the members f which have dissimilar smoking habits One learcut grouping is nonsmokers versus smokers and this qualitative lassifi cation may be further trengthened by requiring that the smoker should be egular smoker igarette smoker or smoker of more than a certain number of igarettes Groups so defined are pure from the conceptual points of view but may on the other hand contain small numbers f individuals Discordance can lso be defined as quantitative intra pair difference between two smoke s A twin pair wher the one member smokes just few cigarettes day and the other 20 cigarettes or more a day is no doubt discordant. The inclu ion f such pairs will increase the number f pairs under study Exposure time expressed age at start of smoking could also be taken into consideration An index of lifetime exposure expressed as number f cigarette years could be developed (cf section 4 3 2) The same principle may be used in forming discordance groups of nondrinkers versus drinkers or quantitative discordance could be measured in terms of absolute lcohol intak as expressed by milliliter of lcohol per month or per year Few variables howeve except the two mentioned above lend themselves to quantitative assessment Physical activity for exampl i basically f the ordinal scale type but may have to be treated as dichotomous for practical purpose

If covariables which have an independent influence on the medical end point studied are ssumed to be present the discordance groups hould if numbers allow be selected from pairs who are concordant with regard to the covariabl in question This principle is termed restriction For exampl the strong correlation between smoking and alcohol drinking should call for study f one discordant variabl t time whil the other is kept constant This situation could be ideal but is seldom met in practice It is possibl however to evaluate to what extent smoking discordant pairs are concordant or discordant in regard to drinking and on the basis of this information to assess the possible bias of the confounding

If possibl internal validity tests of factor discordance should be performed In the present study response facto known to be smoking-related smoker cough was used to evaluate whether measureabl difference existed in the trength of discordance between monozygoti and dizygoti pairs (cf section 7 2)

4 3 *Classification of Dose Variables*

4 3 1 External environmental data

In the first Swedish questionnaire study questions were asked about the subjects lifetime residential histories permitting a rough classification of the respondents according to whether they had resided most of their life in urban or rural areas The categories afforded were lived almost entirely in large towns lived almost entirely in small towns or almost as many years in urban as in rural areas and lived almost entirely in rural areas

The meaning of this urban-rural classification cannot be expressed in very clear terms It may to some degree reflect an exposure to environ mental air pollution but it may just as well reflect *life-style* parameters associated with urban or rural social environments

A different approach was taken in the study on the US twins Each respondent was asked to fill out a table stating the number of years after 1945 that he had spent at different locations within the US At the same time the respondent was asked whether he was living and working respec tively in a downtown suburban or rural area The information was used to set up different kinds of urban-rural exposure scores of which some utilised only the information contained in the individual's report s to type of area The details of the computation procedure have been described (Hrubec et al 1973) The indices were also used to establish discordance groups In the most recent Swedish questionnaire study the same type of questions about lifetime residontial history were used This information has not been utilised for any analysis thus far

4 3 2 Habitual data

Smoking habits

The main smoking classification in the twin research program in Sweden was based on questions asked in the very first qu stionnaire survey The subjects were asked whether they were smokers or nonsmokers about the type of smoking and whether their cigarette consumption was 1 10 11 20 or more than 20 cigarettes per day The classification of discordance in regard to smoking was performed according to the following prin iple

Two groups were formed One group contained nonsmokers versus cig rette smokers regardless of other type of smoking The other group contained pairs of twins where both members were cigarett smokers but with differences in regard to the amount of cigarettes smoked The low groups were cigarette only" smokers while in the higher groups cigar or pipe smokers were also allowed The contrasts as to cigarette smoking pe day were the following

Low smokers	—	High smokers
≤10 cigarettes	—	>10 cigarett s
≤20 cigarettes	—	>20 cigarettes

In many analyses the groups of nonsmokers ve sus cigarette smoke s a e pooled with groups of low smokers versus high smokers Thes pooled groups are designated as pooled low group and pooled high group

Although slight diff rences in the phrasing of the questions exist between the first Swedish questionnaire and the f llowing questionnaire studies in Sweden as well as in the US the principles of forming smok ing discordance groups have been the same

It should be stated here that in some tabulations f discordance groups current and former smokers have been taken togethe while in other subgroupings only current smokers or former smokers have been presented Which principle has been f llowed will be stated clearly in the result sections of this report

In the clinical tudy by Lundman (1966) different concept of smoking discordance was used. On the basi of more detailed explor tion of the subjects smoking habits during the years Lundman calculated a cigarette xposure index which he named number of cigarett years The cigarette consumption of the subject was measured as the lifetime exposure which i the product f the mean number of cigarettes smoked day and the number f years the subject had been smoking The lassification of discordance was then based on the intrapair difference gi ing quanti tative measure of discordance

Drinking

In the questionnair surveys questions on drinking habits were introduced for the first time in 1967 I formation about present habits was lassified for each type of lcoholi beverag beer wine and strong liquor The subjects were sked to state how often they indulged in drinking these kind f beverage and how much they drank each time

In addition to these questions the respondents we asked whethe they ften sometimes or neve on ingl occasion drank as much as half bottl f strong liquo or one bottl f wine or in the American tudy four quart f beer This question led to dichotomy of the subjects into two lasses namely those who had answered never and those who admitted that they often or sometimes had drunk this much on ingle occasion

I the clinical study by Myrhed (1974) lcohol discordance was evaluated i more detail on the basis of grams of lcohol year f hi interview f the twin subjects Myrhed also identified certain behaviors related to high consumption such as blackouts use of eyeopeners drinking behavior parties intoxication hangove well as the above mentioned questions about drinking certain quantity on ingl occasion

Another va iabl f considerable interest for the lassification of lcobol behavi could be measured in the Swedish twin sampl In Sweden all persons who have been in conflict with the police in connection with lcohol abuse such as publi misdemeanors drunken driving or boot legging re egistered by the uthoriti These ecords were screened f ll mal twins belonging to the registry Accordingly the twins could be lassified as registered" or "nonregistered and the pairs concordant or discordant The biological implication f registration annot be straightforwardly evaluated The variabl was shown to be learly related to other measures f excessive alcohol consumption but it must lso be sumed that the variabl i not direct measure of

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1) Thi is not true f the discordance lassification in mortality tudy on US twins (f section 8 3 4)

4 3 Classification of Dose Variables

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≤10 cigarette	---	>10 cigarettes
≤20 cigarette	---	>20 cigarettes

In many analyses the groups of nonsmokers versus cigarette smoker are pooled with groups of low smokers versus high smok rs These pooled groups are designated as pooled low group and pooled high group

was sought as to the use of tonics and vitamins prescription-free analgesics leeping pills tranquillizer and oral contraceptives for women In the dichotomy f these variables the cutoff point was placed between regular use during longer or shorter periods versus now and then and never"

alcohol consumption but certainly of a life-style parameter (Tibblin 1972) It should be kept in mind that the variable may be closely related to social class and that negatives by no means can be regarded as nonalcoholics

Physical activity

In the questionnaire of the old Swedish Registry the different response categories as to amount of physical exercise were respectively no exercise some exercise regular exercise and hard physical training A dichotomy was employed with the cutoff point between some exercise and regular exercise In the US questionnaire the questions specified physical exercise (outside of work) after 35 years of age Persons responding "hardly any or light exercise i e regular walks light gardening" were classified into one group and those responding that they participated in minor sports (swimming tennis etc) or hard physical training were classified into the other group

The questionnaire mailed to the new Swedish twin registry asked about exercise both at work and during leisure time The physical activity at work was judged according to four categories namely mainly sedentary work work that to a large extent involves standing and walking but no other physical activity" work that involves standing and walking but also lifting and carrying" and heavy manual labor The cutoff point was placed between "mainly sedentary work and the other categories

The activity scale in regard to leisure time was based on a series of questions ranging from hardly any exercise to very hard exercise The cutoff point was placed between not very much exercise and rather much exercise

Change of employer

In both the Swedish and the US questionnaire studies questions were asked about how many times the respondent had changed employer since aged 25 Those in Sweden answering 3 or more times were classified into one group and those with few chang into another group

Food habits

Information on food habits was sought in both the Swedish and th US studies In the present report only 2 items connected to food habits have been included as they are supposed to be related to a life-style pattern These items are cooked food once a day or less and more than 5 cups of coffee a day"

Several attempts were made to classify the subjects not so much according to total food intake in terms of calories as according to type of food yielding such groupings as predominantly vegetable and fruit eaters fish eaters meat eaters etc as such classific tions were assumed to relate to smoking habits

Drug consumption

Consumption of drugs was investig ted only in the new Swedish twin registry and in some subsamples from the gen ral population Information

4 Are you sometime happy or sometimes sad without any special reason?
5 Do you prefer to keep to the background in the company of other peopl ?
6 Do you egard yourself as happy and carefree?
7 Do you often reach decisions too late?
8 Do you often feel tired and restless without any special reason?
9 Do you have lively manner?
10 Can you quickly describe your thoughts in words?
11 Are you often lost in your thoughts?
12 Do you have anything against lling things or asking people fo money for some charitable purpose?
13 Are you extremely sensitive in any respect?
14 Are you ever too restless to it still?
15 Do you keep things to yourself except when in the company of good friends?
16 Do you have any nervous problems?
17 Do you lik to crack jokes and tell funny stori to your friends?
18 Do you usually worry a long time after a distressing incident?

The items within each dimension were scored whereafter the indi idual mean cor was lassified as positive or negative in lation to the logical midpoint f nine-category scale

Another indication f psycho-social disharmony was obtained from question ppearing in the l st Swedish questionnaire tudy Individuals who considered their live to be very stressful were regarded as positive

4 4 Classification of Psycho-Social Data

In the Swedish questionnaire study of 1967/70 and partly in the US study a series of questions was asked in regard to the subject s adjustment to everyday life and occupation The different items were presented in the form of statements to which the respondent could express a firm agreement or disagreement or one of three intermediate scale values designat ing partial agreement uncertainty as to level of agreement and partial disagreement The statements were the following:

1 I think that money has almost always been a problem for me
2 Financially I have not achieved what I have hoped for
3 I have often been annoyed by my inability to set aside work
4 My position has involved too much responsibility
5 My training has not been adequate for the work I am doing
6 I have achieved the position (within my vocation) to which I have aspired
7 My ability and training have been used to the full
8 I have had a lot of difficulty in my marriage
9 My children have been a big problem for me
10 I have always gotten along very well with my parents
11 I have always gotten along very well with other people
12 For the most part I have gotten along well with my coworkers
13 I have often run short of time
14 I have often had difficulty in finding enough time to complete the work assigned to me
15 I have often been restless
16 I have often had difficulties in falling asleep
17 I have often felt somewhat uneasy in my work

Floderus (1974) grouped the items as being reflections of financial problems (1-2) occupational maladjustment (3-7) interpersonal con flicts (8 12) shortage of time (13 14) and unspecific maladjustment (15-17)

In the US study an index of the occupational maladjustment wa cal culated in accordance with principles developed by Likert (see e g Edwards 1957) to form a psycho-social score based on items 2 4 7 12 14 and 17

In the last Swedish questionnaire study on the group of twins born between 1926 and 1958 the psycho-social status of the individuals was measured in a more specific way On the basis of the principles developed by Eysenck and Eysenck (1964) in their psychological inventory cale a modified scale was designed for questionnaire use This scale was assumed to measure two psychological dimensions namely stability and extravertness The details of the procedure in developing the scale have been reported by Floderus (1974)

The subject was instructed to answer yes or no to the following questions

1 Do you like having a lot of things going on around you?
2 Are you often uneasy feeling that th re i something you wa t without knowing what it is?
3 Do you almost always have an answer ready when spoken to?

4 Are you sometimes happy o sometimes sad without any special eason?
5 Do you prefer to keep to the background in the company of other people?
6 Do you regard yourself as happy and carefree?
7 Do you often reach decisions too late?
8 Do you ften feel tired and restless without any special reason?
9 Do you have lively manner?
10 Can you quickly describe your thoughts in words?
11 Ar you often lost in your thoughts?
12 Do you have anything against selling things or asking peopl for money f r some charitabl purpose?
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Another indication of psycho-social disharmony was obtained from question appea ing in the last Swedish questionnaire study Indi iduals ho considered their lives to be very stressful wer regarded as positive

4 5 Classification of Medical Endpoints

4 5 1 Data from the questionnaire surveys

All Swedish questionnaire surveys except the very first one contained questions on the medical status of the individual Of greatest importance were some questions pertaining to cough and coronary heart disease The questions on cough were modified from a similar questionnaire[1] worked out by the College of General Practitioners of the British Medical Research Council (1960) The questions in the twin studies were the following:

1 Do you have a cough regularly or for extended periods of time?
2 For how many months in a row do you cough per year more or less than three months in a row?
3 For how many months in a row do you cough up phlegm from your chest more or less than 3 months in a row?

The subjects were classified as having cough [2] if the answer to the first question was affirmative; as having prolonged cough if the answer to the second question indicated cough for more than 3 months in a row; as having "bronchitis if the answer to the third question di vulged that they coughed up phlegm for more than 3 months in a row

The question on heart symptoms focused on the possibility of diagnosing angina pectoris The questions were somewhat modified but mainly based on the questionnaire worked out by Rose (1962) at the London School of Hygiene and Tropical Medicine and ran as follows

1 Have you ever had any pain or discomfort in your chest?
   (a) No
   (b) Yes

2 When do you feel this pain or discomfort?
   (a) When you are emotionally upset or excited
   (b) When you walk fast or walk uphill
   (c) When you walk at normal speed on level ground
   (d) Under other circumstances

3 What do you do when you feel the pain or fort while you are walking?
   (a) Stop walking or walk more slowly
   (b) Take medicine and continue walking at the same speed
   (c) Continue walking at the same speed without taking medicine

4 If you stop walking regardless of whether you take medicine or not how is the pain or discomfort then?
   (a) The pain usually subsides within 10 minutes
   (b) The pain usually continues for more than 10 minutes

---

1) The phrasing was slightly different in the US study
2) Symptom in quotations designates questionnaire diagnosis

5 Where i the pain or discomfort located?
( ) In the middl f the chest
(b) In the left ide f the chest
( ) In the left rm
(d) In some other place

Two lightly different criteria were used for diagnosing angina pectoris" in regard to the answer to question 2 Common to both of the criteria was that the answer to question 1 should be ffirmative; question 3 should be answered with and not b question 5 with a b or but not d For diagnosi of angina pectoris" used sol ly by Liljefor (1970) it wa required that question 2 should be answered by checking ither b or c and not d I the less restricted diagnosis of angina pectoris used in most reports lternative was regarded as sufficient for making the answer under heading 2 affirmative

Apart from the above-mentioned symptoms the questionnaire employed in the New Swedish Twin Registry sked for information about symptoms of shortness f breath tomach and back disorders severe headache hearing loss and llergic predisposition

As for diseases the 1963 Swedish questionnaire asked f information about present illness or illness occurring during a period of 5 year prio to the questionnaire Information was lso sought as to whether the disease had necessitated an examination by a doctor or hospitalization Among disease included in thi li t were asthma bronchial catarrh heart ttack angina high blood pressure gastric ulcer nervous diseases and diabetes The que tionnaire in Sweden 1967/1970 and the US questionnaire also asked about diseases such s asthma and allergi manifestations

The questionnaire employed in Sweden in 1973 did not give list of earlier disease but asked whether the subjects was suffering or had suff red any long lasting or serious diseases or whether he had leave f absence on the grounds f any disease for any considerable length of time

4 5 2 Data from the medical examinations

The linical examiners used vari ty of tests availabl to them t the well-equipped hospital including radiological examinations of heart and lung function tests like respirometry and exercise electrocardiogram and variety f blood and urine examinations The methods and procedures are described in detail in their reports and will not be taken up in the p esent one The methods will be properly referred to later in conjunction with the presentation of the esults

4 5 3 Gross nd cause-specific mortality

On all cases in the first Swedish questionnaire survey of 1961 mortality has been followed up during the ensuing years Matching has been done t regular interval with de th certificate kept by the Central Bureau f Statistics Besides the underlying and contributory causes of death the certificate which i signed by physician gives information on whether the patient had been treated in hospital Hospital records informa tion from general practitioners and other pertinent information were collected to the extent that they were availabl The cause of death was

then established in the following way: Without knowledge of important covariables such as smoking and drinking habits one physician (de Faire) studied available records and made up a preliminary diagnosis of the cause of death A final evaluation was thereafter made by him and two of the authors (LF and TL) whereby the causes of death was classified according to the WHO International Statistical Classification (ISC) of Diseases Injuries and Causes of Death (1967) Finally it was assigned to one of the following groups:

Cause of death	ISC number
Coronary heart disease	410-414 795
Cerebrovascular disease	430-438
Cancer of the lung	162
Cancer other forms	140-161 163-239
Suicides	E950-E959
Accidents	N800-N999 E800-E949 E960-E999
Other causes	—

4 6 Validity Aspects

4 6 1 Validity of measurements

Data from questionnaire tudies are subjective The validity of subjective measurements stand and falls with the truth of the information given by the indi iduals themselves Several sources of error may oper te of which some are related to the questionnaire and the phrasing of the questions and other to the interplay between the interviewee and the interviewe Perhaps most important are error that may be inhere t to the interviewee himself For retrospective assessment of exposure memory may play a ignificant role but the greatest difficulti seem to be associated with the subject own assessment of what exposure category he may belong to His manner of giving information about himself may lso be influenced by preconceived ideas Ther is often tendency on the part of the interviewee to make himself better in the eyes of the investigato (Cederlöf Friberg and Jonsson 1965; Kelltis et al 1966)

For example in regard to external environmental data such as urban-rural esidence history the memory of say 60 year-old subject may not be good enough for him to state the year precisely He may also ove look shorter periods f urban residence which wer indeed of no ignificance to himself but which might have been important for the investig tor to give him proper rating with regard to possible ir pollution exposure Even more important than the subject s memory or value judgements may be his incere uncertainty as to whether his residential area i lassifiabl as urban suburban or rural

V lidity checks in reg rd to the subject ctual migration patt rn could possibly be made in Sweden on the basi of migration ecords but this procedur would have involved an enormous amount of work It therefor has to be accepted that the report on the residential history may not be too trong measure in the indi idual case but that it t least may aff rd the possibility f making a dichotomous assessment

The accuracy f the exposure index developed on the basis of air pollution measurement estimates in the US study can also be questioned Again ther is no easy way to perform validity evaluation As corre lations between ir pollution indices and medical endpoints were rar ly found the alidity of the lassification may have been weak

As for habitual factors such as smoking and drinking the espondent may have forgotten temporary use f cigarettes or alcohol many years ago The use f lassification brackets like 1 10 cigarettes or 11 20 cigarette in the first Swedish questionnaire study presupposes an average estimate on the part f the espondent that may not be lear to him The spondent may tend to underestimate how much he has smoked well as how much he has consumed alcoholic beverages This underreporting may be subconscious and is likely to occur more often in regard to habits that are socially questionabl such as excessive drinking and drug consumption than in regard to socially accepted habits such as smoking

The only entirely ti factory way to validate the questionnaire response would be to perform some kind of observational studies during the same

then established in the following way Without knowledge of important covariables such as smoking and drinking habits one physician (de Faire) studied available records and made up a preliminary diagnosis of the cause of death A final evaluation was thereafter made by him and two of the authors (LF and TL) whereby the causes of death was classified according to the WHO International Statistical Classification (ISC) of Diseases Injuries and Causes of Death (1967) Finally it was assigned to one of the following groups:

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Other causes	—

Some validity analyses were performed in the Lundman (1966) and Lilje-fors (1970) clinical studies to measure the reliability of the questionnaire diagnosis of cough "bronchitis and angina pectoris The physician (Lundman) reinterviewed the subject in regard to bronchiti and dynamic spirometry was performed to ascertain irway resistance Nitrogen delay washout was determined by multipl breath method in rder to detect uneven ventilation

Out of 23 cases that were lassified as having "bronchitis according to the questionnaire 9 or les than half were so classified ccording to linical anamnesti criteria Out of 343 cases that did not have bron chiti according to the questionnaire 7 or two percent were posi tives This outcome is not unexpected as the criterion for being posi tive i sthe difficult to define whil the criterion for being neg tive is easie to comprehend The relation between the "bronchitis report on the questionnaire and the lung function test MMOD showed that seven f th 23 "bronchiti cases had a decreased lung function I this evaluation howeve 53 cases among the 339 nonbronchitis sub-j cts or 16 percent showed an impaired lung function (Lundman 1966)

An indirect way f measuring the relevance f symptom is to find out to what extent it i related to confirmed causal factor Though logi cally appealing it should be emphasized that if the disease endpoint is only assumed to be related to the causal f ctor the confirmation pe se is not scientific way f validation As smoking is known to relate causally to certain respiratory symptoms an analysis of this kind was performed on data from the twin study The results showed lose rela-tion between the respiratory symptoms and breakdown in regard to smoking habits (cf section 7 2)

An ttempt to alidate the diagnosis angin pectoris wa lso made on empirical data Earlier literature had revealed that this symptom diagnosed by questionnaire administered in personal interviews had good prognostic v lue (Rose 1962; Rose 196) Howeve as the present investigations employed mailed questionnaire methods the questions had to be somewhat modified and shortened in such way that might alter the validity In publication by Cederlöf Jonsson and Lundman (1966) based on questionnaire data well as on the linical examination of smoking discordant pairs by Lundman (1966) it appeared that out of 8 mal patients with angina pectoris according to the quetionnaire 4 were confirmed s manifest ases of coronary heart disease Among 204 mal cases not displaying the symptom according to the questionnaire 2 (1 percent) were linically positive The validity was poor for women A sampl consisting of 69 mal twins from the combined Lundman and Liljefors linical studies (Lundman et l 1971) who had been diagnosed ccording to the questionnaire having angina pectoris were subse-quently linically examined in regard to medical history physical igns and exercise lectrocardiogram The clinical diagnosis of angina pecto-ris was based on the criteria recommended by the WHO expert committee on rterial hypertension and ischemi heart disease (WHO 1963) The ECG test was considered pathological according to the principles in the Minnesota code (Blackburn t al 1960) Lundman t al (1971) eported that depending on what criterion was used in diagnosing angina pecto-ris on the questionnaire (section 4 5 1) the confirmation rate based on the anamnesti finding at the clinic was 22 percent or 33 percent the last figure referring to the more restrictive criterion When the investigators added other igns f coronary heart disease like overt

period of time as the questionnaire was being sent out Personal interviews can hardly be regarded as more reliable; on the contrary the underreporting may be even more pronounced in a personal interview where the subject has to face the interviewer than in a questionnaire This consideration notwithstanding some comparisons which have been made between 140 subjects responses on the 1973 Swedish questionnaire and a subsequent personal interview with thes same subjects (Medlund et al 1977) may be of interest

In regard to the qualitative assessment of smoking - i e whether the subject was a nonsmoker a former or a present smoker - 132 out of 140 subjects or 94 percent gave the same response on the interview as they did on the questionnaire; in only one case could the deviating answer at the time of the interview not be explained by possible changes between the two occasions One indication of the possible extent of underreporting is found in a study by the Swedish Central Bureau of Statistics (1965) Based on questionnaire responses in a sample of 55 000 Swedish men and women the total consumption of tobacco was estimated to be 89 percent of the tobacco goods actually sold during the period in question However this finding could just as well be explained by nonresponse as by underreporting

As to alcohol consumption th quantities reported at the time of the interview consistently tended to be lower than what was stated on the questionnaire Björkman (1971) emphasizes that such discrepancies are most pronounced in regard to excessive consumption and that the mailed questionnaire approach seems to give more valid estimates than a personal interview study

In regard to the covariables used in the twin studies comparisons between questionnaire and interview reports were made only to a limited extent In this context a shortened version of the questions about physical activity correlated well (r=0 87) with an index based on a detailed description of type of activity and degree of exertion Further answers to questions about food habits agreed more than 90 percent between questionnaire and interview The measures of psycho-social instability developed by Floderus (1974) were correlated to consumption of psychotherapeutic drugs It was found that the instability groups showed a strikingly frequent intake of such drugs i e up to four times the intake reported by stable subjects This was asse sed as pointing to a high degree of classification validity

Experience in using questionnaires for medical diagnoses is not very extensive In most studies reported the subject had answered the questionnaire in connection with a personal visit to the hospital or clinic The medical personnel then have a chance to explain difficult questions and to complete qu stions which the subject on the first go-around neglects to answer

The main difficulty with mailed questionnaires may well be that the subject has to classify himself into a series of categories which h may find imprecis and incongruent with his own sense of realitv Granted it is possible to get the respondent to go back and fill in parts that he has missed by mailing the questionnaire to him a second time; nonetheless there is no way of explaining the phrasings of the questions On the other hand it is unlikely that the respondent has major reasons for distorting his answers to medical questions as he may have in regard to habitual variables

4 6 2 Validity of sample and subgroupings

To what extent the twin series in the present program represents the general population depends on several factors One f ctor relates to possible biological environmental and social differences between twins and nontwins Another factor is the very restriction that both twins should be alive as an unbroken pair t the time of their induction into the study Othe questions concern the adequacy of subgroupings and rate f nonresponse

Th question f differences between twins and ingletons has been thoroughly discussed by one of the uthors (Cederlöf 1966) on th basis of comparisons between the twin series and sampl of about 900 singletons in the same age bracket. The twin series used for the epidemiological analysis was found to be highly selected with regard to age and sex Thi fact stems from among othe things differences in mortality rates between twins and ingletons (Essen-Möller 1941) An unpredictable bias with regard to health tatus i thus engendered among the couples in which both partne have survived Thi implies that the calculated prevalence tes even if sex and age-standardized should not be regarded as unbiased estimates of any population parameters On the other hand the empirical comparisons with regard not only to medical data but also to some environmental and soci logical background variables did not reveal any large consistent difference between twins and singletons Howeve trongly the lack f representativeness in regard to age and sex deserves to be emphasized the emarkabl conformity between twins and ingl tons with regard to the ariables under study speaks in favo f broader gene lization than could have been expected priori The twin material lthough not representative for the age and sex structur of the popu-l tion stands in definite rel tionship to the defined population of compl te surviving pairs and i emphatically not selected series

Of major importance is the lidity of the subgroupings of the total material both i egard to zygosity and to the focus-variabl of the study smoking The validity f the zygosity diagnosis has been discussed in anothe context (cf section 3 3) The comparability between the monozygoti and dizygoti series in regard to exposure discordance is crucial howeve and fforts have been made to study to what extent the smoking discordance is the same i the two zygosity groups There are sever l sets f data that can be used for such an evaluation

In the pape by Friberg et l (1973) the question of comparability between monozygotes and dizygotes in regard to smoking discordance were discussed in detail based on data from the 1961 questionnaire as well as the 1967/70 questionnaires The comparability of the groups appea in tabl 4 1 page 50 which i extracted from the data presented There ar no indications f relevant diff rence between monozygotes and dizygotes i any of the age- and sexgroups The time of exposure was not evaluated however and some data from Lundman (1966) might indicate the existence f light difference i total exposur In hi sample of smoking discordant pai mean intr pair diff rence of 259 cigarette year (cf section 4 3 2) for 77 monozygoti pair as gainst 316 cigarette year among 89 dizygoti pairs

coronary heart disease suspect angina pectoris and pathological ECG the confirmation rates were 57 and 62 percent respectively There is all reason to believe that these figures overestimate the validity as part of the subjects clinically examined were screened not only by the ques tionnaire but also by a telephone interview which was not discussed in the report

Another way to elucidate the validity of the symptom is to estimate its prognostic value This was analyzed in the group consisting of all 256 twin pairs where the one partner was diagnosed as having angina pectoris according to the questionnaire while the other partner did not The relative risk of death regardless of cause was 1 8 (40 22 deaths); if only deaths from coronary heart disease were considered the relative risk was 2 5 (15 6 deaths)

In summary it can be concluded that the questionnaire is useful for screening cases with CHD as the sensitivity is quite high If it is used for prevalence studies or effect studies one has to be aware of a high frequency of false positives

An elucidation of the validity of some other symptoms can be taken from the New Swedish Twin Registry where all the questions on symptoms (section 4 5 1) on the 1973 questionnaire were asked in a subsequent interview on a subsample of 140 individuals The agreement was consistent ly between 90 and 100 percent

Gross mortality has an absolute validity provided that all cause of death are reported With some highly insignificant exceptions thi is true for Sweden Since the registry has operated with annual follow-ups of mortality no recorded cases of deaths have escaped notification

As for specific cause of death however there is till room for some inaccuracy In order to study this an investigation was made on the 1 290 twins that had died up to 1973 in the age groups of twins born 1901-1925 (de Faire et al 1976) Apart from the official death records for most cases information was available from hospitals records often including autopsies or at least from local physici ns giving a total number of 1 156 deaths to be evaluated The specific cause of death was assessed based on the official death certificate only as well as based on the compiled information only The statistical treatment of the outcome was expressed in terms of sensitivity i e to what degree the death certificate disclosed the true cause of death according to the compiled information The other measure was the so-called rate of confirmation which starting from the death certificate expressed how reliable the di gnosis is in comparison with the true cause For most diagnoses both sensitivity and rate of confirmation approached 95-100 percent In regard to sensitivity some noteworthy exception should be pointed out Among all cases of leukemia only 81 perce t were recorded on the death certificate; th corresponding rate wa for diabetes mell tus 60 percent and for alcoholic psychosis alcoholism and drug dependence 81 percent Th conclusion stated by the authors wa that Swedish d th certificate data are fairly valid for use in epidemiological studies and mortality statistics with regard to most cancers cerebrovascular disease ischemic heart disease bronchitis asthma and emphysema accidents and suicides but not for diabetes mellitus alcoholism mental disease rheumatic heart diseases and other heart diseases However in selected clinical-epidemiolog cal studi all availabl documents should be collected in every case prior to judging th cause of d th

4 6 2 Validity of sample and subgroupings

To what extent the twin series in the present program represents the general population depends on several factors One facto relates to possibl bi logical environmental and social differences between twins and nontwins Anothe factor is the very restriction that both twins should be live as an unbroken pair at the time of their induction into the study Other questions concern the adequacy of subgroupings and rate f nonresponse

The question f diff rences between twins and singletons has been thoroughly discussed by one of the uthors (Cederlöf 1966) on the basis of comparisons between the twin series and sampl f about 900 ingletons in the same age bracket The twin series used for the epidemiological analysis was found to be highly selected with regard to age and sex This fact stems from among othe things differences in mortality rates between twins and ingl tons (Essen-Möller 1941) An unpredictabl bias with regard to health tatus is thus engendered among the couples in which both partners have survived This implies that the calculated prevalence ates even if se and age-standardized should not be regarded as unbiased estimates f any population parameters On the other hand the empi i l comparisons with regard not only to medical data but also to some environmental and sociological background variables did not reveal any large or consistent differences between twins and singletons However strongly the lack of representativeness in regard to age and sex deserve to be emphasized the remarkabl conformity between twins and singletons with regard to the variables under study speaks in favo of a broader generalization than could have been expected a priori The twin material lthough not representative for the age and sex structure of the population tends in definite relationship to the defined population of complet surviving pairs and is emphatically not selected series

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In the paper by Friberg et al (1973) the question f comparability between monozygotes and dizygotes in regard to smoking discordance were discussed in detail based on data from the 1961 questionnaire as well as the 1967/70 questionnaires The comparability of the groups appear in tabl 4 1 page 50 which is extracted from the data presented There ar no indications f relevant diff rences between monozygotes and dizygotes in ny f the age- and sexgroups The time f exposure was not evaluated however and some data from Lundman (1966) might indicate the existence f light difference in total exposur In hi sampl of smoking discordant pair mean intrapair difference of 259 cigarette years (cf section 4 3 2) for 77 monozygoti pairs as against 316 ciga tte years among 89 dizygoti pairs

Table 4 1 Cigarette Exposure 1967/1970 by Sex Age and Zygosity in Smok ing Discordant Twin Pairs According to the 1961 Questionnaire Study (Part of B series All pairs that answered the questionnaire in 1967/1970)

Nonsmokers versus smokers	Born	DIZYGOTES No of pairs	Non-smokers	Difference	Smokers	MONOZYGOTES No of pairs	Non-smokers	Difference	Sm
Males	1911-25	278	0 6	+6 4	7 0	89	0 9	+7 0	[illegible]
	1901-10	120	0 2	+5 4	5 6	36	0 3	+5 5	[illegible]
Females	1911-25	429	0 3	+6 7	7 0	191	0 5	+6 0	[illegible]
	1901-10	134	0 1	+6 0	6 1	47	0 3	+4 7	[illegible]
Pooled low versus pooled high group		No of pairs	Low		High	No of pairs	Low		H
Males	1911-25	389	2 3	+6 8	9 1	140	3 6	+6 4	1[illegible]
	1901-10	156	1 6	+5 4	7 0	50	1 8	+5 2	7[illegible]
Females	1911-25	495	1 4	+6 3	7 7	231	1 7	+5 6	7[illegible]
	1901-10	151	0 9	+5 7	6 6	51	1 0	+4 3	5[illegible]

Another approach to evaluate possible differences between the zygosity groups was to use the relation between smoking and the questionnaire symptoms cough and prolonged cough (cf table 7 2) It can be seen from the table that there is no general trend that the monozygotic pairs should be less discordant than the dizygotic

Possible error of measurement in regard to the smoking habit may affect the composition of the subgroups concordant nonsmokers discordant smokers and concordant smokers Such possible errors have a greater effect on the discordance group which will contain a certain number of concordant nonsmokers and smokers who have reported themselves as discordant (Friedman 1977) The effect of this error will be reflected in lower relative risks in the discordance group than what would be expected on the basis of the A series analysis The size of this deflation of the risk ratio could be theoretically estimated but so many assumptions are involved that it has been considered hardly justified There is no reason to believe that any error for the responses on smoking is different between the monozygotic and dizygotic series If a difference should exist it seems more reasonable to assume that the monozygotes would mo e often tend to give a too concordant report than would the dizygotes In fact as will be later shown (section 7 3) th risk r tio in regard to mortality in the dizygotic serie is not far from what can be expected on the basis of the A-series analysis

The importance f a high response te for an epidemiologically valid assessment of results has been taken up by several authors (Krueger t al 1970; Kaplan and Col 1970; Elli Endo and Armer 1970) The nonresponse te calculated as the number of twin pairs where non or only one f the partners returned hi questionnaire in relation to the total sampl of located pairs approaches 20-25 percent in some of the tudies The nonresponse rate is not higher than reported in some of the studies using mailed health questionnaires where for exampl Dorn had non-response ate of 32 percent (Kahn 1966) It has been shown (Seltze Bosse and Garvey 1975) that nonsmokers tend to be more willing to return thei questionnaires than smokers or measured as response within ix months lmost 100 percent as against 92 94 percent Thi tendency was also shown to be related to amount smoked among present cigarette smokers in such a way that the heavier smokers were les willing to return the questionnaire p omptly

5 HEREDITARY ASPECTS OF MEDICAL ENDPOINTS AND BIOLOGICAL RISK FACTORS

5 1 Introduction

Some leads for the epidemiological analysis of the possibl health effects of smoking may be obtained by investigating to what extent a certain medical endpoint ha higher probability of occurring in the co-twin of a proband who is trait positive as compared to a co-twin of proband who is trait negative The present paper makes an ttempt to study these rel tions on the basis of the method of analysis generally employed to test th importance f geneti factors in contrast to environmental factors namely the classical twin method" (cf section 2 1 2)

A brief overview will now be given f the pr sent attitude towards the influence f geneti factors on obstructive lung disease lung cance and ischemi heart disease as well as on some bi logical risk factors

For many years chroni obstructive lung disease and especially chronic bronchitis was believed to be entirely secondary to environmental determinants This is under tandabl since air pollutants such as ciga tte smoking dusty f ctories and cities and lung irritants such as gases have been shown to have strong deleterious affect on the lung function Repeated infections by bacteria virus mycoplasma and fungi environmental factors the negative effect of which cannot be denied (Leeder 1975) Howeve during the last few years data has appeared showing that these environmental factors exert mor powerful ffect on the lung function and structure if some prerequisite of possibl genetic origin re met (Higgins and Keller 1975; Larson et al 1970) These factors include irway obstruction lack f immune defence deficiency f inhibitors f proteolyti enzyme and depressed cilary function

Individuals with some degree of airway obstruction early in childhood specially those with sthma are prone to repeated infections and the subsequent development f chronic bronchiti Strong evidence has been put forth to the ffect that asthma and allergic rhinitis occur in families and that they are inherited in some way (Schwartz 1952; Leigh and Marley 1967)

The immune defence is f paramount importance for protection against espi tory infection Persons with some immunoglobulin deficiencies exhibit ecurrent upper respir tory tract infections Selective immunoglobulin A (IgA) deficiency is the most common occurring in one out of 500 to 700 persons (Johansson Högman and Killander 1968; Bachman 1965) In large family whe several members either were deficient or had borde line values f IgA Webb and Condemi (1974) found a relation between the defi iency state and chroni bronchitis and emphysema They suggested an intermediate inheritance of the tr it

Laurell nd Eriksson (1963) and Eriksson (1965) were first to describe the associ tion between lpha-antitrypsin deficiency and emphysema. Numerous reports have later confirmed this association and the heredi tary nature f the trait (Hass 1974; Lonstreth t l 1975; Winzeler

Braun and Grob 1974; Lieberman 1969) The theory is that several proteolytic enzymes in the absence of this inhibitor destroy the lung parenchyma thus producing bronchiectasis and emphysema (Lieberman 1973) These changes favor new infections and inflammations which are the main causes of protease-production The evidence that the homozygotes of $alpha_1$-antitrypsin deficiency have high incidences of chronic bronchitis and emphysema is now very strong It may also be that the heterozygotes with intermediate $alpha_1$-antitrypsin deficiency are predisposed to chronic obstructive lung disease even if this question is still controversial (Mittman Lieberman and Rumsfeld 1974; Cole et al 1976; Cooper et al 1974) The heterozygotes may constitute up to 14 percent of the population

The pathogenesis of chronic bronchitis is thus dependent not only on environmental factors but also on genetic ones In fact there is an important interplay between the inherited traits and the environment

There are no conclusive data as to a genetic influence on the development of lung cancer though a tendency to aggregation of lung cancer in human families in the absence of smoking has been reported (Tokuhata 1964) During recent years data have accumulated which that genetic factors may operate in the development of lung cancer in smokers A summarizing discussion is put forth in the Surgeon General Report (1975) The possibility is pointed out that the enzyme aryl hydrocarbon hydroxylase (AHH) may be genetically determined and may mediate an increased susceptibility to certain carcinogens found in tobacco smoke One find ing along this line is a higher prevalence of subjects homozygous for an allele able to induce high AHH levels among lung cancer patients compared to healthy controls and tumor controls (Kellermann Shaw and Luyten Kellerman 1973)

R cently Cederlöf and Friberg (to be published) observed two monozygotic pairs where both members had died from lung cancer In both pairs one member was classified as smoking 11-20 cigarettes while the other member was smoking cigar and pipe only Expected number of concordant pairs based on age and smoking group specific prevalence rates in the total group of 227 present smoking concordant monozygotes in these age groups was only 0 27 pairs which is ignificantly different from the observed value These data support a hypothesis that genetic factors may interact with smoking in the development of lung cancer Further it should be noted that two of the cases did not smoke ciga ett s but igar and pipe only

The genetic mechanism in coronary heart diseas is of polygenic nature and i also mediated through most of the so-called biological fac tors For instance the erum cholesterol level can be controlled by several gene affecting the absorption synthesis transport and remov l of chole terol in the human body This polygenetic control of biologic l factors must naturally re ult in a continuou distribution of such factors when measured in pop lation Some extremes of a factor e g the Fredrickson type II-A hyperlipoproteinemia may exhibit ingle gene control but in the same individual there must be other factors with are under the common polygenic influence (Fredrickson 1971)

Previous studies performed regarding heredity and coronary heart disease have primarily been concerned with familial aggregation of the disease but investigations dealing with blood pressure glucose tolerance and serum lipids have also been made

A familial aggregation of coronary heart disease has been found to exist (Gertler and White 1954; Thomas 1958; and Hammond Garfinkel and Seidman 1971) Russek and Zohman (1958) compared the family histories of 100 young coronary heart disease patients and those of 100 contr l patients A definite history of ardiovascular disease in one or both parents was found in 67 percent of the patients with coronary heart disease In only 16 percent wer both parents living and enjoying normal health whil in 17 percent one or both parents had died from noncardiac or unknown causes In contr st 40 percent of the control subjects had imilar history f cardiovascula disease in one or both parents while 40 percent indicated that both parents were living and enjoying normal health Thomas (1958) obtained the history of the parents and grand parents of 724 medical tudents t the John Hopkins School of Medicine It wa found that cardiovascula disease was 2 7 times more frequent in offspring f affected parents Retrospective studies of this kind can be criticized ince persons with coronary heart disease ar more likely to be awar f family members with similar symptoms than are unaffected persons

I the prospective tudy of Hammond Garfinkel and Seidman (1971) the elation between coronary heart disease and longevity f parents and grandparents was investigated in 1 000 000 men and women The persons in the study were traced ix years after they had answered a detailed questionnaire The subjects were divided into seven groups according to longevity of their parents and grandparents 18 186 of the men and 7 079 of the women had died from coronary heart disease and a direct correlation was found between the mortality and the longevity-class of parents

Twin studies using unselected larger samples concerning coronary heart disease are ther few In the Danish twin registry (Harvald and Hauge 1970) 352 coronary deaths had occurred up to 1968 The individual concordance r for the male monozygotic pairs 39 percent differed ignificantly from that of the male dizygoti pairs 26 percent. In the female pair the difference was greater 44 and 14 percent respectively The isk f femal monozygotic co-twin dying from coronary occlusion was ignificantly higher than in the dizygotic pair No such differences were found for the mal pair Harvald and Hauge concluded that the occurrence f fatal coronary occlusion seemed to be genetically deter mined to much larger extent in females

There is no doubt that type II-A hyperlipoproteinemia i of genetic origin (Fredrickson 1971) but the ituation of the other types of serum lipids i less well known Some important family studi have been perf rmed on this subject Nikkilä and Aro (1973) have studied 412 first-degree relatives f 101 young survivors f myocardial infarction They found that the mean levels of serum cholesterol and serum trigly- ides were ignificantly higher than in control population but lower than i the index patients Hypercholesterolemia occurred 1.8 times hypertriglyceridemi 1 3 times and combined hyperlipidemia 2 5 times more frequently in rel tives than in controls Goldstein et al (1973) lected 164 hype lipidemi infarct survivor and studied first second-

and third-degree relatives to these index cases There was no correla tion between husbands and wives speaking against a general environ mental effect on lipid levels The authors were able to disclose three types of familial hyperlipidemias all of them associated with premature coronary heart disease

From the twin studies performed by Osborne et al (1959) Meyer (1962) and Jensen et al (1965) evidence has been found for both the genetic and environmental influence of cholesterol and triglyceride levels Twin pairs living together were found to have lower mean intrapair variance compared to those living apart

Concerning other coronary heart disease risk factors such as high blood pressure and diabetes mellitus investigations supporting a genetic influence also exist In twin studies by Osborne et al (1959) and Takkunen (1964) the variability of both systolic and diastolic blood pressure was found to have a strong genetic influence The same has been found regarding diabetes mellitus in studies by for instance Harvald and Hauge (1965) In a study on monozygotic twins discordant with respect to overt diabetes mellitus Cerasi and Luft (1967) found a closely similar insulin response after glucose infusion indicating a genetic influence

5 2 Respiratory Findings

The large scal questionnaire studies on the twins have contributed data on cough that have been used for calcul ting coincidence rates (Cede löf t al 1967) In pair concordant for smoking the coincidence rates were consistently higher than expected and the coincidence was higher among monozygotic pairs than among dizygotic pairs

A special analysis was performed on smoking-discordant monozygotic pair divided into two groups according to the cough -status f the nonsmoking partner On the basi f the conditional probability f "Cough" occurring in concordantly nonsmoking pairs an expected number of cougher could be calculated for the smokers in the two above mentioned groups The esults appear f om tabl 5 1

Tabl 5 1 Expected and Observed Prevalence Rate (pe cent) of Cough Among Smoking Partne s to Co-twins Who Either Had or Had Not the Symptom "Cough Monozygoti P irs

Coughing status in non smoking partner	No at isk	Prevalence t f r coughing" among smoking co-twins per cent Expected	Observed
No cough	497	4	12
Cough	41	24	37

Obviously the smok had an increased isk with a factor of about 3 provided his co-twin was healthy i that the smoke could be assumed not to have the predisposition for the symptom However if he had this predisposition shown by the tatus of hi unexposed partne the increased isk as about 1 5 Of furthe interest i to compare the observed te f 12 percent among the smoking partners of healthy co-twins ith the conditional probability of 24 percent in the group of cough among nonsmokers The figur implies that "heredity" i more important than smoking for the development of the symptom Howeve the predisposed" group is less than ten percent which will produce fewer coughers than does smoking The observations wer confirmed in the Ame ican Twin Study (Cede löf Friberg and Hrubec 1969)

In the new Swedish twin registry the ave age conditional probability for cough among nonsmokers in both males and femal was 17 percent in the monozygoti nd 8 11 pe cent in the dizygoti seri zygosity effect that i ignificant

An indication f hereditary influence on espiratory function was provided by expe iment on seri of nine monozygotic and nine dizygoti twin pai s Camne Philipson and Friberg (1972) tudied tracheo-bronchial learance by external me surements of adioactive test aerosol containing monodisperse fluorinated ethylene propylene parti les tagged with 99mTc The learance patterns wer much more similar between the partner in the monozygoti pair than in the dizygoti pairs between pairs The thors concluded that the results indicate that tracheo-bronchial l rance i to great extent constitutionally determined"

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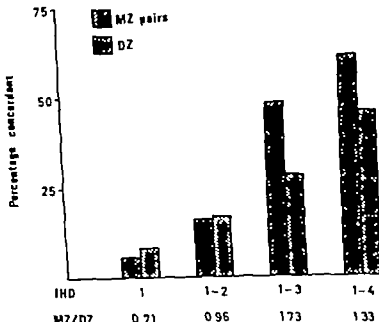


Figure 5 2 Cumul tive concordance rate succes ively including IHD-groups 1-4; IHD-group 1 Myocardial infarction; 2 Angina pecto is ST depression during exercise; 3 Angina pectoris or ST-depression during exer ise; 4 Findings of suspected IHD (From Liljefors 1970)

dizygoti pairs did not diff ignificantly indicating both environmental and geneti influence In regard to triglycerides geneti factors seemed to have greater importance than environmental ones in females

5 3 3 Mortality

The continuous mortality follow-up f the twin registry (cf section 4 5 3) has ffered pos ibility f calculating the influence of genetic factors on gross and cause-specifi mortality

Up to December 1973 2780 deaths 1420 male and 1360 femal had occur red 481 pairs were death concordant and 1818 death discordant Death concordance rates (figure 5 3 page 60) were calculated for coronary heart disease cerebrovascular disease and cance (de Faire Friberg and Lundman 1975) Mal monozygoti twins revealed a ignificantly higher concordance rate for coronary heart disease than the mal dizygoti twins (15 8 vs 8 0 percent) A similar trend was noted among the femal twins but the difference (11 0 vs 7 5 percent) was not ignificant With spect to death from cerebrovascular disease and cancer monozygoti and dizygotic twins displayed only light differences

5 3 Cardiovascular Findings

5 3 1 Morbidity

Analyses on data from the older cohorts of the registry (Cederlöf Friberg and Jonsson 1967) revealed that with the exception of males aged 36-55 the coincidence rate of the symptom angina pectoris according to the *questionnaire diagnosis was higher among monozygotic twins* than among dizygotic ones It was concluded that even though the questionnaire diagnosis angina pectoris to some extent includes cases with unspecific chest pain that cannot be verified clinically the results of the present investigation must be regarded as strongly supporting the idea of a genetic influence on the development of true angina pectoris

In the clinical study by Lundman (1966) the observed coincidence rates for the clinical diagnosis coronary heart disease were 2 2 percent among 92 monozygotic pairs and 1 0 percent among 104 dizygotic pairs as against expected rates of 0 1 and 0 3 respectively The results were based on small numbers however Findings in regard to arcus lipoides corneae usually correlated with CHD revealed a highly significant coincidence of 21 7 percent among monozygotic twin pairs and 5 8 among *dizygotes*

In Liljefors (1970) clinical twin study the hereditary aspects of coronary heart disease were also evaluated When cumulative concordance rates successively including different signs of coronary heart disease were compared it was found that the highest monozygotic/dizygotic ratio was 1 73 This ratio was reached when all signs of clinically overt coronary heart disease were included in the calculation (figure 5 2) In a 7 year follow-up by telephone of the 37 (19 monozygotic and 18 dizygotic) pairs that had been discordant with respect to the pre ence of clinically overt coronary heart disease it was found that 9 monozygotic individuals and 7 dizygotic individuals had developed symptoms of coronary heart disease during the intervening period thus increasing concordance even further (Liljefors 1974)

5 3 2 Biological risk factors

As was pointed out in the literature review the influence of heredity on coronary heart disease is probably of a polygenic nature and consequently many *of the biological risk factors would dis lose a genetic dependence* Of all th clinical twin studi the on by Lundman (1966) on 196 twin pairs is deemed the most suitable for evaluation of the genetic influence of biological ri k factors such as blood pressure and serum lipids on the development of coronary heart di ea e

Analyses of variance were performed for both systolic and diastolic blood pressure and significant F ratios were found for the monozygotic/dizygotic intrapair variance for both males and females This shows that the variability in blood pressure i greatly influenced by genotic factors

When analys s of the same type were applied to serum lipid it was found that the variability of phospholipids was under a strong gen ti in fluence For cholest rol the intrapair v riances for monozygotic and

6 SMOKING AND ITS ENVIRONMENTAL AND HEREDITARY INTERACTIONS

6 1 Introduction

It has long and repeatedly been suggested that smokers differ from non-smokers in regard to some structural as well as behavioral characteristics other than smoking Statistics have revealed that smoking habits are different in different population strata defined for example by sex age and thei background (Friedman et al 1972) Smoking has traditionally been regarded as a mal trait. In Sweden smoking was regarded as socially incorrect behavior for women until about 20-30 years ago Over time this norm has changed The younger generations of females have clearly taken up the smoking habit more and more This seems to be part f cultural pattern and smoking behavior as such has not been suggested to be biologically linked to sex or to age

It is lso apparent from the liter ture that smoking is more common in urbanized areas than in rur l ones Furthermore certain educational and occupational categories show rel tively higher number of smoker than do others (Swedish Central Bureau of Statistics 1965; Haenszel Shimkin and Mills 1956; Cederlöf et l 1975) This may be linked to financial considerations but more likely to life-style factors linked to social inheritance The higher prevalence of smoking in some groups may to some extent have genetic background as it can be reasonably argued that people f certain personality type would prefer to move from the country to the ity from the lowe educational levels of their parents to higher educational levels and that such a personality type would have certain ambitions as to occupation

During the 1950 that is during the time when the first large British and Ame ican prospective smoking tudi began to appear in the literature - some reports were published that suggested differences between smokers and nonsmokers not only in regard to population characteristics and socioeconomi data but also in egard to physiological behavioral and personality va iabl (Heath 1958; Schubert 1958; Lilienfeld 1959) Fisher (1958 1959) advanced hi controversial theory that differences between smoker and nonsmok rs could be f genetic origin and could be associ ted with other geneti mechanisms

More recent reports have documented associations between smoking and sever l characteristics that are lik ly to compete with smoking as risk factors for illness or premature death. Higgins and Kjelsberg (1967) tudied smoker and nonsmokers in regard to social characteristics and physiological variabl They found that smokers consume more alcoholi bevs ages than nonsmokers Thi finding was later confirmed by ourselves using the Ame ican twin registry (Hrubec et al 1973) the old Swedish twi registry (Friberg et l 1973) and smoking study on probability sampl f 55 000 Swedish men and women (Cede löf t al 1975)

Associ ted with the Kaiser Permanente Research Institute in USA (cf Friedman t l 1972 1974) an American research team has published seri f arti les during the last few year comparing smoker and

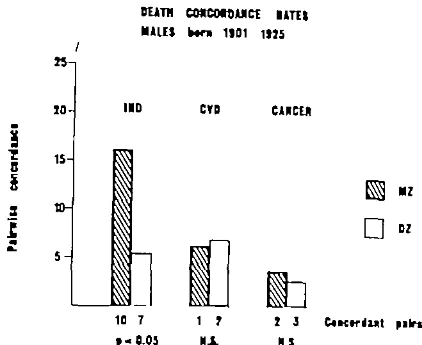


Figure 5 3 Death concordance rates for twin pairs born during 1901 25 males (From de Faire et al 1975)

Since 1971 the Swedish Twin Registry has been matched monthly against the mortality records for all Sweden This has allowed a medical examination of the co-twins of deceased partners within a reasonable time limit (de Faire 1974) Up to 1973 262 pairs became death discordant and 205 of the survivors underwent medical examination where especially clinical signs of coronary heart disease were searched for If there is a genetic compon nt in coronary heart disease the prevalence of coronary heart disease should be high in the most genetically predisposed co-twins that is in the monozygotic co-twins whose partn rs had died from coronary heart disea e Those co-twins whose partners had died from other causes hould have a lower prevalence of coronary h art disea The prevalence of myocardial infarction angina pectori and pathological Q-wave in the ECG in the examined twins was 4/10 in the male monozygotic group whose partners had died from coronary heart disease against 4/25 in the dizygotic group The prevalence was non- ignificantly lower in the group whose partners had died from other caus s If el ctrocardiographic signs of coronary heart disease were also included nearly all monozygotic co-twins were affected A statistical difference between monozygotic twins whose partners died from coronary heart disease and monozygotic twins whose partners had died from other causes w also found

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6 1 Introduction

It has long and repeatedly been suggested that smokers differ from non-smokers in egard to some structural as well as behavioral characteristics other than smoking Statistics have eveled that smoking habits are different in different population strata defined for exampl by sex age and thnic background (Friedman t 1 1972) Smoking ha traditionally been regarded as a mal trait. In Sweden smoking was regarded socially incorrect behavior for women until about 20-30 years ago Over time this norm has changed The younger generations of females have clearly taken up the smoking habit more and more This seems to be part of cultural pattern and smoking behavior as such has not been suggested to be biologically linked to sex or to age

It is also pparent from the literature that smoking is more common in urbanized areas than in rural one Furthermore certain educational and occupational ategories show relatively higher number of smokers than do other (Swedish Central Bureau of Statistics 1965; Hammer 1 Shinkin and Miller 1956; Cederlöf t al 1975) This may be linked to financial considerations but more likely to life-style factor linked to social inheritance The higher prevalence of smoking in some groups may to some extent have genetic background as it an be easonably argued that peopl f certain personality type would prefer to move from the country to the ity from the lower educ tional levels f their parents to higher educational level and that such personality type would have certain ambitions to occupation

During the 1950 that is during the time when the first large British and American prospective smoking studi began to appear in the literature some reports wer published that suggested differences between smokers nd nonsmoker not only in regard to population characteristics and socioeconomi data but also in regard to physiological behavioral and personality variabl (Heath 1958; Schubert 1958; Lilienf ld 1959) Fisher (1958 1959) advanced his controversial theory that differences between smokers and nonsmokers could be f geneti origin and could be associ ted with other genetic mechanisms

More recent reports have documented sociations between smoking and several characteristics that are likely to compete with smoking as risk factors for illness premature death Higgins and Kj lsberg (1967) tudied smoker and nonsmoker in egard to social characteristics and physi logical ariabl They found that smokers consume more lcoholic beverages than nonsmokers This finding was later confirmed by ourselve using the Ame ican twin registry (Hrubec t 1 1973) the old Swedish twin egistry (Friberg t 1 1973) and smoking tudy on probability sampl f 55 000 Swedish men and women (Cederlöf et al 1975)

Associated ith the Kaiser Permanente Research Institute in USA (cf e g F iedman t 1 1972 1974) an American research team has published seri f arti 1 during the last few years comparing smoker and

nonsmokers in regard to exposure to occupational risk factors (Friedman Siegelaub and Seltzer 1973) consumption of alcoholic beverages and coffee (Friedman Siegelaub and Seltzer 1974) use of oral contraceptives and drugs (Seltzer Friedman and Siegelaub 1974) etc The results were based on large samples and in many respects showed obvious differences between smokers and nonsmokers

Possible psychosomatic differences between smokers and nonsmokers have been observed in regard to for example pain tolerance (Seltzer et al 1974) and electroenphalographic pattern (Brown 1973) Probably the most well-known psycho-social characteristics related to smoking are the so-called type A and type B behavioral patterns which were first described by Friedman and Rosenman (1959) On the basis of his personality inventory Eysenck (1965) reported that smokers have a more pronounced extraverted behavior than nonsmokers Floderus (1974) modified Eysenck s personality inventory for use in connection with mailed questionnaire investigations She showed among other things that the neuroticism dimension of the scale is also clearly related to smoking in such a way that smokers show on an average a more unstable psychological status

6 2 Structural and Behavioral Characteristics of the Smoker

6 2 1 Introductory remarks

Apart from first section presenting smoking in relation to sex and age the present part of the chapter will report data on the relation between smoking and a serie of behavioral characteristics Data have been taken mainly from the new Swedish twin registry covering the cohorts born 1926 to 1958 and occasionally from the older part of the registry covering the cohorts born 1901 to 1925

Data will be presented in both A-series and B-series fashion The A series analysi will disclose the generally appearing difference between smokers and nonsmokers as unrelated individuals The B-series analysis aims t disclosing to what extent A-series ratios between smokers and nonsmokers prevail or become educed in the B-series indicating the degree of control or the gain in group comparability achieved by using twin pairs (cf section 2 2 2) For the last mentioned analysis only part f the availabl pairs have been used namely those pairs where both partners are concordant nonsmoker or concordant present cigarette smokers or where the one membe is a nonsmoker and the other i present igar tte smoker This estriction has been made because smoking amount i difficult to assess in groups where the cigarette smoking is combined with other types of smoking Furthermore there is no unobjectionable way to equalize numbers of cigarettes to diff rent amounts of pipe smoking Former smokers have also been excluded due to the problems they would pose in egard to quantitative asse sment.

In the following sections the A-series tabl will present prevalence rates among nonsmokers by sex and ge as well ratios of the prevalence r te in different smoking groups ove the prevalence rate of nonsmokers All tes ar age-adjusted on the basi of five-year intervals the weights being based on the age distribution among nonsmokers The statistical testing is performed on the 5-percent level and on the directed lternate hypothesis that ratios are above unity The A-series tables re denoted by an A after the tabl number

The B-series tables display only ratios which ar adjusted fo diff rences with regard to sex ge nd smoking distribution in the subgroupings the weights being based on the distributions of sex age and smoking in the combined discordance groups The statistical testing is also here performed on the 5-percent level and on the directed alternate hypothe is that the discordance groups show lower ratios than the ratio of concordant smokers ove concordant nonsmokers The B-series tables have the same number the corresponding A-serie tables but are denoted by B

Th numbers t isk in the A- and B-series analyses ar presented in tabl 6 1A and 6 1B page 64 respectively

Table 6 1A Numbers at Risk by Sex and Age in Different Smoking Groups; New Swedish Twin Registry A-series

	Born	Non-smokers	Cigarettes only ≤7	8-15	≥16	Cigarettes and pipe	Pipe only	Former smokers
Males	1956-58	1037	67	65	7	78	18	103
	1946-55	1758	250	588	246	853	179	543
	1926-45	2831	339	743	577	1130	676	1346
Females	1956-58	1036	208	150	12	-	-	103
	1946-55	2173	682	1251	296	-	-	652
	1926-45	4875	815	1761	540	-	-	1207

Table 6 1B Numbers at Risk in Different Smoking Concordance and Discordance Groups; New Swedish Twin Registry B-series

Group	No of Pairs
Concordant Nonsmokers	4117
Concordant Smokers (Present cigarette smokers only)	1770
Discordant Smokers (Present cigarette smokers vs nonsmokers)	1350
- Monozygotes	340
Dizygotes	1010

6 2 2 Selected data on education and employment

It appears from table 6 2A that among present smokers a significant number has a lower education than nonsmokers while there is no relation between former smoking and educational level The ratios do not show any convincing relations to amount smoked nor do they indicate differences between age and sex groups The B series groups (table 6 2B page 66) deviate significantly from the A-series ratio 1 24 and are close to unity regardless of zygosity

All items concerning employment show significant relations to present smoking and in several subgroups also to former smoking The highest and markedly dose related ratios are found for employment in th age group born 1956-58 By and large shiftwork and piecework seem to be dose related in most but not all subgroups over time The values in the B-series analysis (table 6 2B) do not show any control

Tabl 6 2A Selected Data on Education and Employment by Sex and Age; Age-adjusted Ratios in Smoking Groups in Relation to Prevalence Rates Among Non-smokers; New Swedish Twin Registry A-seri

	Born	Non-smokers	Cigarettes only ≤7	8-15	≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate		Ratio			Ratio	
Elementary school only								
Males	1946-55	29 3	1 2	1 4	1 3	1 2	1 0	1 0
	1926-45	44 3	1 2	1 3	1 1	1 2	1 2	0 9
Females	1946-55	25 0	1 3	1 6	1 6			0 9
	1926-45	51 2	1 1	1 1	1 1			0 9
Employed								
Males	1956-58	7 5	2 2	3 9	(9 5)	4 4	(3 7)	1 4
	1946-55	58 2	1 2	1 3	1 2	1 2	1 0	1 2
	1926-45	88 4	1 0	1 0	1 0	1 0	1 0	1 0
Females	1956-58	3 3	4 4	6 5	(17 7)		-	2 6
	1946-55	55 2	1 1	1 1	1 3			1 0
	1926-45	60 5	1 1	1 1	1 2			1 0
Overtime								
Males	1946 55	19 4	0 9	1 1	1 7	1 5	1 3	1 1
	1976-45	32 8	1 0	0 9	1 3	1 1	0 9	1 1
Femal	1946-55	10 2	1 0	1 0	1 4			1 2
	1926-45	8 9	1 0	1 1	2 0			1 1
Shiftwork								
Males	1946-55	19 2	1 2	1 4	1 5	1 6	1 6	1 1
	1926-45	19 2	1 2	1 2	1 4	1 6	1 7	1 3
Femal s	1946-55	9 7	1 4	1 4	2 0			1 3
	1926-45	9 0	1 2	1 6*	1 6			1 2
Piecework								
Mal	1946-55	39 6	1 1	1 2	1 3	1 3	1 1	1 2
	1926-45	38 2	1 3	1 2	1 0	1 3	1 2	1 1
Femal	1946-55	11 8	1 2	1 5	1 8			1 4
	1926-45	12 6	1 2	1 6	1 7			1 1

Table 6 2B Selected Data on Education and Employment; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers in Discordant Groups	
		DZ	MZ
Elementary school only	1 24	1 03	0 96
Employed	1 06	1 09	1 10
Overtime	0 86	1 41	1 23
Shiftwork	1 27	1 11	1 04
Piecework	1 17	1 13	1 27

6 2 3 Selected data on alcohol consumption

In the A-series analysis both drinking and excessive drinking (table 6 3A) turn out to be strongly correlated to smoking in all smoking groups The dose gradient is most clearly seen for excessive drinking but also exists especially in the youngest age groups for alcohol drinking in total There is an obvious relation to age for both items which also shows up among cigarette plus pipe smokers and pipe only smokers In most subgroups former smokers show rates similar to the lowest amount group among present smokers but the relation is significant throughout

The control of the alcohol items is strong and significant for both dizygotic and monozygotic twins (table 6 3B) Although the control is significant meaning that the ratios in the zygosity groups are reliably lower than those found between concordant smokers and concordant nonsmokers the ratios especially for excessive drinking are obviously well above unity The B-series analysis from the cohorts 1901-1925 is also included in the table and the same tendency can be seen for them

Table 6 3A Selected Data on Alcohol Consumption by Sex and Age; Age-adjusted Ratios in Smoking Groups in Relation to Prevalence Rates Among Nonsmokers; New Swedish Twin Registry A-series

	Born	Non-smokers	Cigarettes only ≤7	8-15	≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Alcohol drinking								
Males	1956-58	13 1	3 2	5 9	(5 4)	5 2	(5 9)	3 8
	1946-55	66 5	1 3	1 4	1 4	1 4	1 4	1 3
	1926-45	67 1	1 3	1 3	1 4	1 4	1 3	1 3
Femal	1956-58	17 8	3 3	4 2	(3 7)			2 9
	1946-55	57 8	1 4	1 4	1 5			1 3
	1926-45	46 6	1 4	1 5	1 7			1 5
Excessive alcohol drinking								
Males	1956-58	2 0	9 0	16 9	(14 3)	22 5	(19 5)	7 3
	1946-55	13 3	2 6	2 9	3 2	3 3	2 4	2 5
	1926-45	5 5	3 2	3 5	5 1	4 0	2 6	2 2
Femal	1956-58	1 1	9 2	21 2	(30 3)			7 1
	1946-55	1 8	3 7	5 6	12 6			3 5
	1926-45	0 5	4 2	8 6	21 9			5 3

Table 6 3B Selected Data on Alcohol Consumption; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smoker versus Nonsmokers in Discordant Groups DZ	MZ
Born 1926-58			
Alcohol drinking	1 48	1 22	1 09
Excessive lcohol drinking	4 49	1 74	1 49
Born 1901 25			
Alcohol drinking	2 05	1 26	1 22
Excessive lcohol drinking	6 53	2 08	1 72

Table 6 2B Selected Data on Education and Employment; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers in Discordant Groups	
		DZ	MZ
Elementary school only	1 24	1 03	0 96
Employed	1 06	1 09	1 10
Overtime	0 86	1 41	1 23
Shiftwork	1 27	1 11	1 04
Piecework	1 17	1 13	1 27

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The control of the alcohol items is strong and significant for both dizygotic and monozygotic twins (table 6 3B) Although the control is significant meaning that the ratios in the zygosity groups are reliably lower than those found between concordant smokers and concordant nonsmokers the ratios especially for excessive drinking are obviously well above unity The B series analysis from the cohorts 1901-1925 is also included in the table and the same tendency can be seen for them

6 2 4 Selected data on drug consumption

Among the drugs selected for analysis tonics and vitamins were supposed to be "healthy" and to relate negatively to smoking This is confirmed to some extent by the outcome among present smokers (table 6 4A) With few exceptions the r tes in lmost all subgroups are unity or below unity The values for the former smokers are never below unity

Prescription-free analgesics sleeping pill and tranquillizers are all related to present as well as former smoking Among present cigarette smokers the relation to amount is most clearly seen fo tranquillizers but also exists for the ther drugs in this group There is no obvious sex difference Although the rate for former smokers on an average are lower than those for smokers with the highest amount of cigarettes they nonetheless are very often increased significantly

Oral contraceptives are ignificantly and markedly related to presently well as forme ly smoking women The highest ratios are found in the youngest femal group but the prevalence among nonsmokers is ratha low throughout An increased ratio is seen also in women who smoke 7 cigarettes or less day

The B-series analysis (tabl 6 4B) shows a certain amount f control for prescription-free analgesics sleeping pills and oral contraceptives The last mentioned drug shows significant indeed almost ideal control in both zygosity groups

Tabl 6 4B Selected Data on Drug Consumption; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers in Discordant Groups	
		DZ	MZ
Tonics and vitamins	1 01	0 92	0 94
Prescriptionf ee analgesics	1 28	1 04	1 17
Sleeping pills	2 34	1 36	1 85
Tranquillizers	1 87	1 60	1 77
Or l contr ceptives	2 21	1 19	0 98

Table 6 4A Selected Data on Drug Consumption by Sex and Age; Age-adjusted Ratios in Smoking Groups in Relation to Prevalence Rates Among Nonsmokers; New Swedish Twin Registry A series

	Born	Non-smokers	Cigarettes only			Cigarettes and pipe	Pipe only	Former smokers
			≤7	8-15	≥16			
		Prevalence Rate		Ratio			Ratio	
Tonics and vitamins								
Males	1956-58	36 0	0 8	0 8	(1 6)	0 7	(1 5)	1 0
	1946-55	26 1	0 8	0 8	0 7	0 9	0 8	1 1
	1926-45	23 4	0 9	0 8	0 6	0 9	0 8	1 1
Females	1956-58	42 3	1 1	1 1	(1 4)	-	-	1 3
	1946-55	48 9	1 0	1 0	0 9	-		1 1
	1926-45	49 5	0 9	0 9	0 9	-		1 2
Prescription-free analgesics								
Males	1956-58	11 9	1 0	2 6	(2 4)	2 1	(0 9)	1 6
	1946-55	13 2	1 2	1 5	1 7*	1 8	1 4	1 5
	1926-45	21 8	1 1	1 2	1 3	1 3	1 1	1 2
Females	1956-58	25 9	1 3	2 0	(1 0)	-		1 5
	1946-55	36 7	1 0	1 1	1 3			1 1
	1926-45	37 7	1 0	1 2	1 3		-	1 2
Sleeping pills								
Males	1956-58	0 7	4 3	0 0	(0 0)	3 7	(0 0)	0 0
	1946-55	1 0	3 3	1 1	2 7	3 5	1 7	2 1
	1926-45	2 8	0 8	1 5	2 2	2 3	1 4	1 2
Females	1956-58	0 9	1 6	6 7	(0 0)	-		2 1
	1946-55	2 2	1 3	2 0	5 0			1 8
	1926-45	5 2	1 7	2 1	3 4		-	1 5
Tranquillizers								
Males	1956-58	1 7	0 9	1 8	(8 4)	3 8	(0 0)	0 0
	1946-55	3 5	1 5	1 1	2 1	1 8	1 4	1 8
	1926-45	5 8	1 6	1 8	2 1	2 1	1 5	1 5
Females	1956-58	2 7	1 4	2 7	(3 1)		-	1 8
	1946-55	5 6	1 4	1 9	3 6	-	-	1 6
	1926-45	13 9	1 3	1 6	2 4	-		1 3
Oral contraceptives								
Females	1956-58	1 8	4 0	8 9	(9 3)			4 8
	1946-55	19 6	1 5	1 7	1 7			1 3
	1926-45	11 3	1 3	1 6	2 0		-	1 4

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Oral contraceptives are ignificantly and markedly related to presently as well as formerly smoking women The highest tios are found in the youngest femal group but the prevalence among nonsmokers is ther low throughout An increased tio is seen also in women who smoke 7 cigarettes or less day

The B-series analysi (table 6 4B) shows a certain amount of control for prescription-free analgesics leeping pills and oral contraceptives The last mentioned drug shows ignificant indeed almost ideal control in both zygosity groups

Table 6 4B Selected Data on Drug Consumption; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers in Discordant Groups	
		DZ	MZ
Tonics and vitamins	1 01	0 92	0 94
Prescriptionfree analgesics	1 28	1 04	1 17
Sleeping pills	2 34	1 36	1 85
Tranquillizers	1 87	1 60	1 77
Or l contraceptives	2 21	1 19	0 98

Table 6 4A *Selected Data on Drug Consumption by Sex and Age; Age-adjusted Ratios in Smoking Groups in Relation to Prevalence Rates Among Nonsmokers; New Swedish Twin Registry A-series*

	Born	Non-smokers	Cigarettes only			Ciga rettes and pipe	Pipe only	Former smokers
			≤7	8-15	≥16			
		Prevalence Rate		Ratio			Ratio	
Tonics and vitamins								
Males	1956-58	36 0	0 8	0 8	(1 6)	0 7	(1 5)	1 0
	1946-55	26 1	0 8	0 8	0 7	0 9	0 8	1 1
	1926-45	23 4	0 9	0 8	0 6	0 9	0 8	1 1
Females	1956-58	42 3	1 1	1 1	(1 4)	-	-	1 3
	1946-55	48 9	1 0	1 0	0 9	-	-	1 1
	1926-45	49 5	0 9	0 9	0 9	-	-	1 2
Prescription free analgesics								
Males	1956-58	11 9	1 0	2 6	(2 4)	2 1	(0 9)	1 6
	1946-55	13 2	1 2	1 5	1 7	1 8	1 4	1 5
	1926-45	21 8	1 1	1 2	1 3	1 3	1 1	1 2
Females	1956-58	25 9	1 3	2 0	(1 0)	-	-	1 5
	1946-55	36 7	1 0	1 1	1 3	-		1 1
	1926-45	37 7	1 0	1 2	1 3		-	1 2
Sleeping pills								
Males	1956-58	0 7	4 3	0 0	(0 0)	3 7	(0 0)	0 0
	1946-55	1 0	3 3	1 1	2 7	3 5	1 7	2 1
	1926-45	2 8	0 8	1 5	2 2	2 3	1 4	1 2
Females	1956-58	0 9	1 6	6 7	(0 0)	-		2 1
	1946-55	2 2	1 3	2 0	5 0			1 8
	1926-45	5 2	1 7	2 1	3 4	-	-	1 5
Tranquillizers								
Males	1956-58	1 7	0 9	1 8	(8 4)	3 8	(0 0)	0 0
	1946-55	3 5	1 5	1 1	2 1	1 8	1 4	1 8
	1926-45	5 8	1 6	1 8	2 1	2 1	1 5	1 5
Females	1956-58	2 7	1 4	2 7	(3 1)	-		1 8
	1946-55	5 6	1 4	1 9	3 6	-		1 6
	1926-45	13 9	1 3	1 6	2 4	-	-	1 3
Oral contra-ceptiv s								
Females	1956-58	1 8	4 0	8 9	(9 3)	-		4 8
	1946-55	19 6	1 5	1 7	1 7			1 3
	1926-45	11 3	1 3	1 6	2 0			1 4

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Tabl 6 4B Selected Data on Drug Consumption; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmoke in Discordant Groups	
		DZ	MZ
Tonics and vitamins	1 01	0 92	0 94
Prescriptionfree analgesics	1 28	1 04	1 17
Sleeping pills	2 34	1 36	1 85
Tranquillizers	1 87	1 60	1 77
Oral contraceptives	2 21	1 19	0 98

Table 6 5A Selected Data on Psycho-social Items by Sex and Age; Age-adjusted Ratios in Smoking Groups in Relation to Prevalence Rates Among Nonsmokers; New Swedish Twin Registry A-series

	Born	Non smokers	Cigarettes only ≤7	Cigarettes only 8-15	Cigarettes only ≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Instability								
Males	1956-58	11 2	1 6	2 1	3 8	2 1	2 0	1 6
	1946-55	13 9	1 5	1 5	2 2	1 7	1 5	1 6
	1926-45	12 0	1 6	1 6	1 8	1 8	1 6	1 3
Females	1956-58	23 0	2 1	2 2	1 8	-	-	1 7
	1946-55	24 8	1 3	1 7	2 2	-	-	1 3
	1926-45	22 3	1 4	1 5	2 0	-	-	1 2
Extravertness								
Males	1956-58	69 7	1 2	1 0	1 2	1 2	1 2	1 0
	1946-55	60 7	1 1	1 1	1 1	1 1	1 0	1 0
	1926-45	55 6	1 2	1 1	1 2	1 1	1 0	1 0
Females	1956-58	54 7	1 1	1 1	1 2	-	-	1 2
	1946-55	46 2	1 2	1 2	1 2	-	-	1 1
	1926-45	42 9	1 2	1 2	1 3	-		1 1
Sleeping difficulties								
Males	1956-58	19 9	1 5	2 0	1 4	1 7	1 4	1 4
	1946-55	11 9	1 6	1 8	2 3	1 7	2 2	1 3
	1926-45	10 2	1 4	1 7	1 9	2 1	1 6	1 2
Females	1956-58	26 3	1 4	1 8	1 6		-	1 3
	1946-55	17 2	1 4	1 6	2 2	-	-	1 1
	1926-45	15 4	1 4	1 6	2 3			1 2
Stress								
Males	1956-58	9 2	0 7	0 7	1 6	2 1	0 6	1 5
	1946-55	13 6	1 2	1 2	1 9	1 4	1 4	1 0
	1926-45	17 5	1 1	1 2	1 5	1 3	1 3	1 2
Females	1956 58	11 0	1 3	1 3	1 5			1 0
	1946-55	13 4	1 0	1 2	1 7	-		1 0
	1926-45	11 1	1 2	1 4	2 1			1 2
Divorced								
Males	1946-55	0 4	0 0	2 0	4 0	1 8	1 1	0 8
	1926-45	2 7	2 3	2 3	4 0	2 8	1 2	0 9
Females	1946-55	0 7	0 8	2 8	4 3	-		1 4
	1926-45	3 9	1 1	2 4	4 4			1 2

Tabl 6 5A. (continued)

	Born	Non smokers	Cigarettes only ≤7	8-15	≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate		Ratio			Ratio	
Change f employer ≥3 times								
Males	1946-55	20 6	1 5	1 8	2 1	1 8	1 6	1 5
	1926-45	16 5	1 3	1 4	1 3	1 3	1 3	1 3
Females	1946-55	25 2	1 1	1 3	1 7			1 2
	1926-45	11 7	1 1	1 2	1 4			1 3
Low physical activity								
Males	1956-58	6 2	3 4	4 0	(6 9)	4 5	(0 9)	2 2
	1946-55	16 0	1 2	1 9	2 8	1 9	1 6*	1 2
	1926-45	17 2	1 1	1 5	2 3	1 7	1 3	1 0
Females	1956-58	9 7	1 7	3 3	(4 3)			2 0
	1946-55	20 8	1 2	1 8	2 4		–	1 2
	1926-45	22 8	1 0	1 5	2 1		–	0 9
Cooked food once day or less								
Males	1956-58	5 3	1 4	3 2	(5 4)	3 2	(2 1)	0 9
	1946-55	27 8	1 2	1 2	1 4	1 2	1 2	1 0
	1926-45	37 0	1 1	1 2	1 2	1 1	1 1	1 0
Females	1956-58	11 2	1 5	2 5	(3 0)			1 0
	1946-55	50 9	1 1	1 1	1 3			1 0
	1926-45	41 1	1 2	1 2	1 4			1 1
Coffee > 5 cups day								
Males	1956-58	4 5	2 3	3 1	(0 0)	2 8	(4 9)	1 9
	1946-55	16 2	1 2	2 0	2 8	2 5	2 1*	1 6
	1926-45	32 2	1 3	1 6	1 9	1 8	1 8	1 3
Females	1956-58	4 1	3 2	4 4	(10 2)			2 1
	1946-55	12 6	1 4	2 7	4 2*			1 6
	1925-45	32 6	1 2	1 7	2 0			1 2

6 2 5 Selected data on psycho-social and related items

Among the items analyzed (table 6 5A) only two are psycho-social in the narrow sense of emanating from psycho-metric scaling namely instability and extravertness Some other items indicate unstabl behavior that might be personality related such as leaping difficulties stress and divorce Frequent change f employer low physical activity cooked food once day or less and 5 cups of coffee a day or more may be assumed to relate in some way to psycho-social factors

Table 6 5B Selected Psycho-socially* Related Items; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers In Discordant Groups	
		DZ	MZ
Instability	1 81	1 32	1 18
Extravertness	1 15	1 20	1 01
Sleeping difficulties	1 77	1 39	1 29
Stress	1 36	1 19	1 02
Divorced	2 70	1 85	1 25
Change of employer ≥3 times	1 40	1 15	0 81
Low physical activity	1 64	1 57	1 20
Cooked food once a day or less	1 32	0 96	1 17
Coffee ≥5 cups a day	1 75	1 90	1 44

It is obvious that whatever item is studied positives occur more frequently among present smokers and in some cases among former smokers as well With the exception of extravertness all items are also related to amount of cigarettes smoked These tendencies are strongest for divorce and instability There are no obvious sex or age differences except possibly a tendency to higher ratios in the youngest cohort

It is noteworthy that most of these items are rather well controlled in the B-series (table 6 5B) Instability shows a decrease from 1 8 to 1 2 which is significant Divorce is also markedly controlled in the B-series

6 3 Hereditary Aspects

6 3 1 Introductory remarks

The degree of control or in other terms the increased comparability between smokers and nonsmokers in twin pairs is most certainly an ffect of early environment the social heredity" but may also be a esult of true genetic det rminants One way to discriminate between an environmental and a geneti influence is to use the so-called clas ical twin method meaning a comparison of monozygotes and dizygotes in regard to concordance rates In the case of compl te ascertainment i when all twin pairs including the concordantly negatives have been observed the concordance r te can be replaced by the coincidence rate (cf section 2 1 2) It is lso possibl to calculate an expected coincidence rate on the assumption f andom combinations This tio between observed and expected coincidence i the gross effect of social and genetic heredity In the statistical testing the chi-square test for heterogeneity has been used Whenever the r tio is highe for monozygotic twins some extra resemblance between the partners in such pai s i indicated This extra esemblance may be due either to genetic influences or to a social heredity that is tronger for monozygotic than for dizygoti twins The difference between monozygoti and dizygotic pairs in regard to the trength f the association has here been evaluated by a tatistical test of third-orde interaction (Kastenbaum and Lamphiear 1959) The difference is expressed as quotient between the ratios for MZ and DZ respectively

The f llowing sections f the present chapter show coincidence r te for ll items presented in earlier sections Furthermore ttempts have been made to test the hypothesis that the habitual items should be dependent on social and/or geneti heredity and hence lso show increased tios among nonsmokers in twin pair where the partner is smoke compared to tios among nonsmokers in conco dantly nonsmoking pairs (NET-analysis)

6 3 2 Heredity of smoking

Observations that the smoking habit i more concordant in monozygoti than in dizygoti twins have been reported by Friberg t l (1959) by Shields (1962) and by Cederlöf (1966) in a publication based on the old Swedish twin egi try

Table 6 6 page 74 hows that with one singl exception ll sex and age groups have ignificantly increased r tios for observed over expected coincidence tes It is also seen that the quotients ar ignificantly higher for monozygoti than for dizygoti twins which may be interpreted as evi dence f geneti component or f tronger environmental pressure for conformity

6 3 3 Selected data on education and employment

The amount f formal education as well as diff rent items elated to employment show observed coincidence ratios that are ignificantly greate than expected throughout (tabl 6 7 page 74) Consistently the quotients are ignificantly higher among monozygotes as compared to dizygotes

The hypothesis that education and employment items in the nonsmoking partners should be related to the smoking status of the co-twin (NET analysi) did not eceive support (table 6 8 page 75)

Table 6 5B Selected "Psycho-socially" Related Items; Sex and Age Standardized Ratios between Smokers and Nonsmokers in Concordant Groups in Comparison to Discordant Groups by Zygosity; New Swedish Twin Registry B-series

	Concordant Smokers versus Concordant Nonsmokers	Smokers versus Nonsmokers In Discordant Groups	
		DZ	MZ
Instability	1 81	1 32	1 18
Extravertness	1 15	1 20	1 01
Sleeping difficulties	1 77	1 39	1 29
Stress	1 36	1 19	1 02
Divorced	2 70	1 85	1 25
Change of employer ≥3 times	1 40	1 15	0 81
Low physical activity	1 64	1 57	1 20
Cooked food once a day or less	1 32	0 96	1 17
Coffee ≥5 cups a day	1 75	1 90	1 44

It is obvious that whatever item is studied positives occur more frequently among present smokers and in some cases among former smokers as well With the exception of extravertness all items are also related to amount of cigarettes smoked These tendencies are strongest for divorce and instability There are no obvious sex or age differences except possibly a tendency to higher ratios in the youngest cohort

It is noteworthy that most of these items are rather well controlled in the B-series (table 6 5B) Instability shows a decrease from 1 8 to 1 2 which is significant Divorce is also markedly controlled in the B series

Table 6 8 Selected Data on Education and Employment; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Non-smok rs Grouped by Smoking Status of Co-twin; New Swedish Twin Registry MIT series

		Non-Smokers	Present Cigarette Smokers	All Present Smokers	Former Smokers
No t risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Elementary school only	MZ	1 00	1 04	1 04	0 95
	DZ	0 98	1 04	1 03	0 90
Employed	MZ	1 01	0 96	0 97	1 06
	DZ	0 98	1 07	1 07	1 09

6 3 4 Selected data on alcohol consumption

Both items on drinking particularly excessive drinking (table 6 9 page 76) show observed coincidence tes that are far above expectation and considerably higher among the monozygoti twins

The hypothesis that nonsmoking partners of smoking co-twins should have increased ratios is strongly verified for both monozygoti and dizygoti twins (tabl 6 10 page 76) The ratios for the monozygotes are by far the strongest especi lly in regard to exces ive drinking Increased ratios are also found among partners to former smokers

6 3 5 Selected data on drug consumption

The observed coincidence ratios are markedly higher than those expected for the drug consumption items (tabl 6 11 page 77) as well most so for tranquillizers The differences between the two zygosity groups are ignificant throughout

The MIT-analysis (tabl 6 12 page 77) shows markedly increased ratios for leeping pills but generally negative results for the other items

6 3 6 Selected data on psycho-social and related items

The coincidence ratios (tabl 6 13 page 78) are increased throughout and in almost ll cases ignificantly so The quotients are also significant in most cases

In the MIT-analysi (table 6 14 page 79) the nonsmoking partners of presently smoking co-twins show increased prevalence ratios for every item i this category The finding holds true in both zygosity groups

Table 6 6 "Heredity" of Smoking; Coincidence Ratios and Quotients between MZ and DZ Ratios by Sex Age and Zygosity; New Swedish Twin Registry

	Coincidence Ratios Observed/Expected MZ	DZ	Quotients MZ/DZ
Males			
1926 45	1 46	1 20	1 22
1946–55	1 68	1 26	1 33
1956–58	4 00	2 67	1 50
Total	1 61	1 32	1 22
Females			
1926–45	1 71	1 41	1 21
1946–55	1 65	1 33	1 24
1956 58	2 78	2 18	1 28
Total	1 76	1 44	1 22

Table 6 7 Selected Data on Education and Employment; Coincidence Ratios and Quotients between MZ and DZ Ratios by Sex and Zygosity; New Swedish Twin Registry

	Coincidence Ratios Observed/Expected MZ	DZ	Quotient MZ/DZ
Elementary school only			
Males	1 73	1 48	1 17
Females	1 83	1 51	1 21
Employed			
Males	1 34	1 33	1 01
Females	1 33	1 26	1 06
Overtime			
Males	2 24	1 86	1 20
Females	4 17	1 89	2 21
Shiftwork			
Males	3 26	2 61	1 25
Females	4 80	2 44	1 97
Piecework			
Males	2 22	1 71	1 30
Females	4 49	3 30	1 36

Table 6 8 Selected Data on Education and Employment; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Non smokers Grouped by Smoking Status of Co-twin; New Swedish Twin Registry NET-series

		Non-Smokers	Present Cigarette Smoker	All Present Smokers	Former Smokers
No t risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Elementary school only	MZ	1 00	1 04	1 04	0 95
	DZ	0 98	1 04	1 03	0 90
Employed	MZ	1 01	0 96	0 97	1 06
	DZ	0 98	1 07	1 07	1 09

6 3 4 Selected data on alcohol consumption

Both items on drinking particularly excessive drinking (tabl 6 9 page 76) show observed coincidence r tes that are far above expectation and considerably higher among the monozygoti twins

The hypothesis that nonsmoking partners of smoking co-twins should have increased ratios is strongly verified for both monozygoti and dizygotic twins (table 6 10 page 76) The ratios for the monozygotes are by far the strongest especially in egard to excessive drinking Increased ratios are lso found among partners to former smokers

6 3 5 Selected data on drug consumption

The observed coincidence atios are markedly higher than those expected for the drug consumption items (table 6 11 page 77) as well most so for tranquillizers The differences between the two zygosity groups are significant throughout

The NET-analysis (tabl 6 12 page 77) shows markedly increased ratios for leeping pills but generally negative results for the other items

6 3 6 Selected data on psycho-social and related items

The coincidence ratios (tabl 6 13 page 78) are increased throughout and in almost all cases ignificantly so The quotients are also significant in most cases

In the NET analysis (table 6 14 page 79) the nonsmoking partners of presently smoking co-twins show increased prevalence ratios for every item in this category The finding holds true in both zygosity groups

Table 6 9 Selected Data on Alcohol Consumption; Coincidence Ratios and Quotients between MZ and DZ Ratios by Sex and Zygosity; New Swedish Twin Registry

	Coincidence Ratios Observed/Expected		Quotients
	MZ	DZ	MZ/DZ
Alcohol drinking			
Males	1 46	1 34	1 09
Females	1 44	1 34	1 07
Excissive alcohol drinking			
Males	4 96	3 30	1 50
Females	13 12	6 12	2 14

Table 6 10 Selected Data on Alcohol Consumption; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-twin; New Swedish Twin Registry NET-series

		Non-Smokers	Present Cigarette Smokers	All Present Smokers	Former Smokers
No at risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Alcohol drinking	MZ	0 93	1 32	1 36	1 45
	DZ	0 93	1 25	1 23	1 15
Excessive alcohol drinking	MZ	0 80	2 81	3 48	2 28
	DZ	0 66	2 00	2 05	1 19

Tabl 6 11 Sel cted Data on Drug Consumption; Coincidence Ratios and Quotients between MZ and DZ Ratios by Sex and Zygosity; New Swedish Twin Registry

	Coincidence Ratios Observed/Expected MZ	DZ	Quotients MZ/DZ
Tonics and vitamins			
Males	2 19	1 92	1 14
Females	1 48	1 23	1 20
Prescriptionfree analgesics			
Males	2 57	1 87	1 37
Females	1 63	1 32	1 23
Sleeping pills			
Males	3 04	2 34	1 30
Females	4 64	2 90	1 60
Tranquillizers			
Mal	7 64	3 73	2 05
Females	3 29	2 84	1 16
Or l contraceptives			
Females	2 94	2 02	1 46

Tabl 6 12 Selected Data on Drug Consumption; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rate Among Nonsmokers Grouped by Smoking Status of Co-twin; New Swedish Twin Registry MET-series

		Non-Smokers	Present Cigarette Smoker	All Present Smokers	Former Smokers
No t risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Tonics and vitamins	MZ	1 01	0 97	0 96	1 06
	DZ	0 99	1 00	0 99	1 11
Prescriptionf ee analgesics	MZ	1 00	0 98	1 02	1 16
	DZ	0 98	1 02	1 01	0 95
Sleeping pills	MZ	0 70	1 42	1 75	1 03
	DZ	0 84	1 37	1 33	1 02
Tranquillizers	MZ	0 95	1 06	1 16	0 94
	DZ	1 02	0 99	1 01	1 02

Table 6 13 Selected Data on Psycho-social and "Psycho-socially Related Items Coincidence Ratios and Quotients between MZ and DZ Ratios by Sex and Zygosity; New Swedish Twin Registry

	Coincidence Ratios Observed/Expected		Quotients
	MZ	DZ	MZ/DZ
Instability			
Males	3 50	2 04	1 72
Females	2 17	1 49	1 46
Extravertness			
Males	1 22	1 09	1 12
Females	1 44	1 18	1 22
Sleeping difficulties			
Males	2 96	1 34	2 21
Females	2 34	1 42	1 65
Stress			
Males	2 75	2 07	1 33
Females	3 11	1 96	1 59
Divorced			
Males	4 69	4 30	1 09
Females	5 12	2 85	1 80
Change of employment >2 time			
Males	2 49	2 13	1 17
Females	2 67	2 36	1 13
Low physical activity			
Males	2 96	1 71	1 73
Females	2 20	1 54	1 43
Cooked food ≤ once a day			
Males	2 17	1 96	1 11
Females	1 60	1 46	1 10
Coffee > 5 cups a day			
Males	2 59	1 72	1 51
Females	2 30	1 65	1 39

Table 6 14 Selected Data on "Psycho-social and "Psycho-socially" Related Items; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-twin; New Swedish Twin Registry NST-series

		Non-Smokers	Present Cigarette Smokers	All Present Smokers	Former Smokers
No t risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Instability	MZ	0 95	1 56	1 46	1 39
	DZ	0 98	1 13	1 12	0 85
Extravertnes	MZ	0 99	1 14	1 17	0 93
	DZ	1 01	1 02	1 02	0 97
Sleeping difficulties	MZ	0 98	1 39	1 24	1 12
	DZ	0 96	1 15	1 12	0 92
Stress	MZ	0 91	1.25	1 19	1 23
	DZ	0 93	1 11	1 15	1 04
Divorced	MZ	0 79	2 03	1 82	0 64
	DZ	0 87	1 11	1 18	0 91
Change of employer >3 times	MZ	0 94	0 99	1 13	1 21
	DZ	0 91	1 22	1 25	1 13
Low physical activity	MZ	0 90	1 15	1 23	1 02
	DZ	1 02	0 96	1 04	0 79
Cooked food once day or less	MZ	1 01	1 06	1 03	1 10
	DZ	0 97	1 18	1 14	0 98
>5 cups of coffee day	MZ	0 97	1 01	1 18	1 04
	DZ	1 01	0 96	0 98	1 08

7 THE SMOKING RELATED DISEASE PANORAMA

7 1 Introduction

The aim of this report has not been to present an extensive survey of the vast literature in the fi ld of tobacco and health Such surveys have been made continuously by the US Publi Health Service starting with the first report to the Surgeon General in 1964 Reviews have also been given by the Royal College f Physicians in London (1962 1971) and most recently by WHO Expert Committee (1975)

The majority of investigations have shown tatistical associ tions between the smoking habit and an extensive series f diseases and causes f death Even if the earliest epidemiological investigations have been rightfully criticized for being of the retrospective type and being based on nonrandom sampling their main results have been confirmed in later more sophisticated investig tions

The main target of many earlier investigations was cigarette smoking men but published investig tions during recent years have indicated increased risks for women (Wynder 1972; Silverberg and Holleb 1973; Born 1974) and for smokers of igars and pipe (Gsell and Abelin 1972) A recently published investigation from Sweden (Cederlöf et al 1975) with appropriate techniques f sampling and data collection has demonstrated that within equal smoking groups the hypermortality among women approaches that of men and that pipe and igar smokers experience a considerably increased isk especially f lung cancer

Few scientists today seem to question the gathered evidence of a cause and effect relationship between lung cancer and smoking Also in twin tudies there has ecently come up evidence that lung cancer i associated with smoking both in monozygotic and dizygotic smoking discordant twin pairs (Cederlöf and Friberg to be published) These data will be commented upon in section 8 3 3

As for coronary heart disease a report from the Wo ld Health Organization (WHO 1975) considers cigarette smoking an important cause of an increased isk f ischaemic heart disease contributing both to the atherosclerot i process itself and to the condition that precipitates heart ttack and determines f tal outcome The conclusions are based on epidemiological evidence as well as experimental data mostly in connection with carbon monoxide exposure. A study of particular relevance seems to be the one by Anderson t al 1973 who found that volunteers with coronary heart disease exposed during 4 hours to between 60-120 mg CO/m^3 giving rise to carboxyhaemoglobin-levels of 3-5 percent in exercise tests showed symptoms f angina pectoris earlier than when breathing pure air

In a large scal follow-up on the mortality of British doctors (Doll and Peto 1976) the well-known association between smoking and coronary heart disease was again confirmed. The authors conside the very high mortality tios in young age groups to great extent caused by smoking while they are much more cautious concerning the relationship at higher

ages Here it is considered possible that much of the excess mortality from ischaemic heart disease in this group of men arises not because of an effect of smoking but because smoking correlates with some other factor which contributes directly to the disease If however smoking is a major cause of ischaemic heart disease in young men it would seem likely that it also contributes to causing the disease in the old

Multifactorial etiology has been more and more emphasized where the importance of physiological risk factors such as hypertension and hypercholesterol have been pointed out (Epstein 1965 1967; Keys et al 1972; Biörck 1975; Keys 1975) Very little has been investigated in regard to habitual factors such as drinking and drug consumption to which however attention has been drawn more recently (Higgins Kjelsberg and Metzner 1967; Klatsky Friedman and Siegelaub 1973 1974; Seltzer Friedman and Siegelaub 1974; Friedman et al 1975) On a Swedish population sample (Cederlöf et al 1975) the influence of registration for alcohol abuse as well as urban-rural residence appeared to be related to death from coronary heart disease among nonsmokers as well as smokers

Although the multifactorial etiology has been well recognized the confounding effects of competing risk factors for the assessment of the causal relationship between smoking and disease have generally been disregarded

Twin investigations into the questions of tobacco smoking and health not related to the present program are very few in previous literature The only major ones have been performed on the Danish registry compiled in 1954 (cf section 3 1 3)

A publication by Hauge et al (1968) considered mortality and morbidity in relation to tobacco consumption among 904 smoking discordant same-sexed twin pairs where both partners were alive on January 1 1959 After 7 years of follow-up 114 deaths were recorded among whom 66 belonged to the heavier smokers and 48 to the lighter The presentation did not consider zygosity The excess deaths were mainly caused by coronary occlusion where 27 cases had occurred among heavier smokers as against 13 among lighter smokers In regard to morbidity there were no noteworthy differences in regard to angina pectoris and non-fatal coronary occlusion while claudication chronic bronchitis and ulcers were more prevalent among the heavier smokers

In a short publication in 1970 it was stated by Hauge Harvald and Reid without any presentation of actual data that neither MZ nor DZ pairs showed any tendency to increased mortality in the heavier smoking co-twins When the material was subdivided according to cause of death no conspicuous exception from the general pattern was found but the sub-groups were relatively small

In regard to selected diseases it was stated that fatal coronary occlusions and non-fatal occlusions diagnosed in hospitals showed only a slight and non-significant tendency to be associated with higher tobacco consumption and in MZ pairs where only one co-twin had an occlusion he was equally often the heavier smoking as the light smoking one Symptoms of angina pectoris and chronic bronchitis however showed significant differences between the smoking groups but it was not reported whether in the monozygotic the dizygotic or both series

7 2 Twin Studies Morbidity

7 2 1 Introductory remarks

When the twin program was initiated in 1961 the main objective was the follow-up of mortality The only feasible way of approaching the indi viduals in the study was by mailed questionnaires Littl was known t that time as to the possibilities f obtaining valid information on morbidity with the aid of self-administered questionnaires The British Medical Research Council Committee on the Etiology of Chronic Bronchitis had developed a tandardized questionnaire on respiratory symptoms and Rose in England had tried to diagnose ischemic heart pain by the aid of questionnaires in field surveys (cf section 4 5 1) Both questionnaires had been designed for use by interviewer and had to be modified to be of any value in mailed questionnaire survey where the number of questions is critical for the response rate

In spite f the questionable validity it was decided to modify these questions and to use them tentatively together with series of other medical questions in the mailed surveys of 1963 in Sweden and 1967 in both Sweden and the United States Further questions on morbidity were included in the questionnaire f the new Swedish twin registry (Hedlund et al 1977) Details on the phrasing of the questions as well as on some validity aspects are given in Chapter 4

As complement to the more extensive questionnaire studies a number of linical investigations on morbidity was performed by Lundman (1966) and Lilj fors (1970) The following sections will summarize the results in regard to respiratory symptoms cardiovascular symptoms and some other medical findings

7 2 2 Respiratory findings

The operationally defined symptoms cough and prolonged cough (cf section 4 5 1) were investigated in all twin studies A summarized sur vey of the findings is given in the A-series fashion in tabl 7 1 page 84 It should be pointed out that the smoking categories differ somewhat between the US and Swedish tudies and also between the two Swedish studies

Independent f sex age and country both symptoms are clearly related to the numbe of cigarettes smoked among present smokers The gradient is consistently teepe for the symptom prolonged cough in comparison to cough although the prevalence is lower The values for former smokers are lower than those for present smokers throughout but in many sub-groups somewhat above unity If the results from the US and Swedish tudies are compared given igarette consumption is generally associated with higher atios in the Swedish than in the American tudy For example males born 1911 1925 and smoking more than 10 cigarettes a day in Sweden display ratio of 6 4 in regard to cough which is the same as for smokers f more than 30 cigarette in USA The ratios for "pro-longed cough are in the quoted smoking categories 13 4 in Sweden and 8 1 in USA

Smoking of cigarettes and pipe and of pipe only also show ratios well above unity which is especially notabl for the younger Swedish age group

ages Here it is considered possible that much of the excess mortality from ischaemic heart disease in this group of men arises not because of an effect of smoking but because smoking correlates with some other factor which contributes directly to the disease If however smoking is a major cause of ischaemic heart disease in young men it would seem likely that it also contributes to causing the disease in the old

Multifactorial etiology has been more and more emphasized where the importance of physiological risk factors such as hypertension and hypercholesterol have been pointed out (Epstein 1965 1967; Keys et al 1972; Biörck 1975; Keys 1975) Very little has been investigated in regard to habitual factors such as drinking and drug consumption to which however attention has been drawn more recently (Higgins Kjelsberg and Metzner 1967; Klatsky Friedman and Siegelaub 1973 1974; Seltzer Friedman and Siegelaub 1974; Friedman et al 1975) On a Swedish population sample (Cederlöf et al 1975) the influence of registration for alcohol abuse as well as urban-rural residence appeared to be related to death from coronary heart disease among nonsmokers as well as smokers

Although the multifactorial etiology has been well recognized the confounding effects of competing risk factors for the assessment of the causal relationship between smoking and disease have generally been disregarded

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In a short publication in 1970 it was stated by Hauge Harvald and Reid without any presentation of actual data that neither MZ nor DZ pairs showed any tendency to increased mortality in the heavier smoking co-twins When the material was subdivided according to cause of death no conspicuous exception from the general pattern was found but the subgroups were relatively small

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Table 7 2 "Cough and "Prolonged Cough by Sex Age and Smoking Discor dance Groups in the Old Swedish and the American Twin Registries B-series

	Born	DIZYGOTES No of Pair	DIZYGOTES Pooled Low Group	DIZYGOTES Pooled High Group	MONOZYGOTES No f P irs	MONOZYGOTES Pooled Low Group	MONOZYGOTES Pooled High Group
SWEDISH REGISTRY							
"Cough							
Males	1911 25	408	16	60	155	12	17
	1901 10	170	13	29	62	1	13
Females	1911 25	514	26	63	235	19	32
	1901 10	165	15	32	53	5	10
"Prolonged cough							
Males	1911 25	408	2	20	155	5	11
	1901 10	170	6	11	62	0	5
Females	1911 25	514	10	27	235	5	10
	1901 10	165	4	12	53	1	3
AMERICAN REGISTRY							
Cough							
Males	1917 27	725	52	122	493	30	74
Prolonged cough							
Males	1917 27	725	32	80	493	21	47

The B-series analyses covering the total pooled low and high groups only is shown in table 7 2 There is consistent difference between the two exposur groups both among dizygotes and monozygotes The ratios (not displayed in the table) are about the same in both zygosity groups Although the rates are clearly dependent on age there is no consistent interaction between ge and smoking ffect. Nor is any difference seen between males and females Despite higher smoking discordance in the American registry on an average about 17 opposed to 7 cigarettes in the Swedish study the tios are if any thing less in the American series than in the Swedish

The symptom cough in the ld Swedish twin registry was also evaluated in interaction with smoking and urban-rural residential history (Cedar löf 1966) The prevalence of respir tory symptoms was higher among concordantly smoking men in urban than in rural areas in the A-analysis as well as in the B-analysis In concordant nonsmokers however there was no difference t all between the areas This was interpreted as speaking in favor of specifi urban factor interacting with smoking

Thi problem was further lucidated in the study on American twins (Hrubec t l 1973) A series f indices to be correlated with respiratory symptoms was developed on the basis of questionnaire reports on residential history and official US statistics with regard to air pollution

Table 7 1 Age-adjusted Morbidity Ratios for Cough and Prolonged Cough by Sex Age and Smoking Groups in the Swedish and American Twin Registries (Prevalence among Nonsmokers) A-series

		No at Risk		Cough		Prolonged Cough	
		Males	Females	Males	Females	Males	Females
SWEDISH REGISTRIES							
Born 1946-55							
Nonsmokers		1758	2173	3 0	2 8	-[1]	-
Present cgts	< 7	250	682	2 1*	2 2*	-	-
	8-15	588	1251	2 7	3 7	-	
	>16	246	296	4 4	8 0	-	
Cigarettes and pipe		853	-	4 3	-	-	
Pipe only		179	-	3 6	-	-	-
Former smokers		543	652	1 2	1 7	-	
Born 1926-45							
Nonsmokers		2831	4875	2 9	4 1	-	-
Present cgts	< 7	339	815	1 7	1 2	-	
	8-15	743	1761	3 6	2 4	-	-
	>16	577	540	4 6	4 2	-	-
Cigarettes and pipe		1130	-	3 8	-	-	
Pipe only		676	-	2 1	-	-	-
Former smokers		1346	1207	1 3	1 4	-	-
Born 1911-25							
Nonsmokers		1456	4207	3 5	4 5	0 7	0 7
Present cgts	<10	1041	975	3 6*	2 7*	5 1*	4 9*
	>10	635	285	6 4	5 5	13 4	15 0
Former cgts	<10	324	242	1 3	0 8	1 7	0 6
	>10	200	38	1 0	(1 2)	1 4	
Born 1901-10							
Nonsmokers		741	2909	6 7	6 0	2 5	1 7
Present cgts	<10	457	239	2 2*	2 7*	2 6*	3 8*
	>10	189	67	5 1	5 2	6 3	7 0
Former cgts	<10	178	70	1 0	1 7	0 8	2 6
	>10	90	8	0 6	(1 5)	0 8	(5 3)
AMERICAN REGISTRY							
Born 1917-27							
Nonsmokers		865	-	4 3	-	2 2	-
Present cgts	<10	297	-	1 5	-	1 5	-
	11-30	1435	-	3 6	-	4 4	-
	>30	566	-	6 4	-	9 1	-
Cigar and pipe only		255	-	1 7		2 0	
Former smokers		889	-	0 7	-	3 8	

1) Not studied

Smoking in relation to coronary heart disease was investigated clinically in the Lundman study (1966) There was no evidence of excess morbidity from overt coronary heart disease in the smoking twins no of any differences between smokers and nonsmokers regarding post exercise ST changes indicating coronary insufficiency In tabl 7 3 page 86 are given the number of concordant and discordant pair with respect to coronary heart disease and in elation to smoking exposur Coronary heart disease was considered as diagnosed if the person had clinical history of previous myocardial infarction or coronary insufficiency (ST >0 5 mm horizontal or downward loping) There were 8 pair 4 MZ and 4 DZ with concordant coronary heart diseases findings and 29 pairs 9 MZ and 20 DZ with discordant coronary heart disease findings In 6 of the MZ pairs it was the nonsmoking partner who had the positive findings and in 3 it was the smoking partner For the DZ pairs the corresponding figures were 11 and 9 respectively

Since both high blood pressure and high serum cholesterol and tri glyceride levels are associated isk factors fo coronary heart disease hypothesis could be that one should find higher lipid values and higher blood pressure among the smoking twins in the smoking discordant pairs However the analysi in the present study showed only weak association between smoking and the serum lipids cholester l and tri glycerides; their levels were lightly lower in the smoking twins The smokers had lower mean weight by around 3 kg

Systolic and diastolic blood pressure howed consistent tendency to be lower in the igarette exposed twins in both the monozygotic and di zygotic groups The di stolic blood pressure in rel tion to smoking is given in figure 7 4 It i evident that prolonged cigarette smoking was not associated with persistent levation f the blood pressure

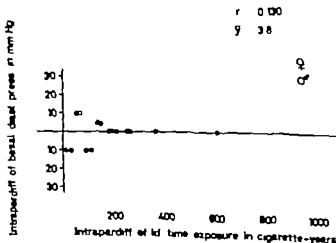


Figure 7 4 Correlation between I trapair Diff rences for Smoking Exposure and Basal Diastoli Pressure in 37 Smoking Discordant Monozygotic Pairs (Correlation Coefficient; ӯ Mean of Intrapair Difference) (from Lundman 1966)

compiled by the former National Air Pollution Control Administration in Research Triangle Park USA One of these indices took into account the number of years the subject had lived in certain areas and the average air pollution measured Another index considered only the subjects own reports as to how many years they had lived in downtown suburban or rural areas Only the last mentioned index related to the prevalence of the respiratory symptoms This relation was found in the A-series analyses but not in the B-series Due to low numbers the implication of the negative finding was considered limited

In the Lundman study (1966) based on 92 monozygotic and 104 dizygotic same-sexed smoking discordant pairs aged 37-77 years the degree of uneven ventilation according to a nitrogen washout delay method correlated well with cigarette consumption The forced vital capacity (FVC) and forced expiratory volumed during 1 sec ($FEV_{1.0}$) were significantly lower for smokers in a manner correlated with the amount of cigarette consumptio The differences found were as high as or higher than had previously been reported between smokers and nonsmokers The lung function was affected to the same extent in males and females These results were found among both monozygotic and dizygotic twins

7 2 3 Cardiovascular findings

Former reports from the twin registries in regard to the mailed questionnai studies have mainly focused on the symptoms operationally defined as angina pectoris (cf section 4 5 1) From the A-series analyses male smokers appeared to have a significant hypermorbidity ratio of 1 6 while female smokers did not show any significant hypermorbidity In the American study current smokers of 30 or more cigarettes a day showed a hypermorbidity of 2 3 and former smokers a hypermorbidity of 1 9 both figures statistically significant The B series analysis on the Swedi h twins did not show any hypermorbidity ratio in any zygosity group while that on the American series showed a significant hypermorbidity ratio of 1 6 in the dizygotic twins No hypermorbidity was seen in th monozygotic twins

Table 7 3 Number of Concordant and Discordant Pairs by Zygosity with Respect to Coronary Heart Disease in Relation to Smoking Exposure (from Lundman 1966)

		Exposed					
		MZ			DZ		
		+	-	total	+	-	total
	+	4	6	10	4	11	15
Not exposed	-	3	24	27	9	38	47
	total	7	30	37	13	49	62

\+ Coronary heart disease (see text)
\- No coronary heart disease

	Psycho-social item compared to partner is		
	More	Equal	Less
Conflicts at work	6	16	2
Ambition t work	10	11	3
Overtime t work	8	12	4
Dedication to work	11	9	4

$p < 0.05$ Infarction   No infarction

Figure 7 5 Intrapair Difference for Psycho-soci 1 Items in 24 Infarction Discordant Pairs (Infarction Partner Compared to "Healthy" Partner) (Condensed from Liljefors 1970)

Coronary heart disease in male twins was studied from another point of departure by Liljefors (1970) Twin pairs were selected on the basis of positive replies on the questionnaire from the one or both twins in regard to angina pectoris (for one or both members in the pairs) Among 91 pairs 89 could be classified with regard to the presence or absence of coronary heart disease Thirty-five pairs were found to be coronary heart disease discordant 23 pairs coronary heart disease concordant and 31 pairs healthy concordant Of the coronary heart di sease discordant pairs 27 were discordant with respect to myocardial infarction but in 10 of these pairs the partner had angina pectoris or other signs of coronary heart disease The smoking habit in the Liljefors study was found to be almost the same among the 35 coronary heart disease discordant pairs 77 percent of the diseased and 74 percent of the healthy twins being present or former smokers When the coronary heart disease concordant pairs were compared with healthy concordant pairs significantly more of the coronary heart disease pairs were found to be smokers 89 against 74 percent

On the basis of a personal interview the social background and psycho-social strain during adult life of 24 infarction discordant pairs 20-40 years of age were classified according to a point scale The most interesting results were found regarding psycho-social strain at work in matters such a conflicts ambition and overtime The two latter factors were combined and this score was added to the score dedication to work As is seen in figure 7 5 consistently more of the twins with a myocardial infarction had some psycho-social strain compared to their healthy partners For ambition the difference reached statistical significance

The importance of drinking and several other factors for the assessment of the relationship between smoking and angina pectoris was analyzed jointly on the Swedish and American twin series (Hrubec Cederlöf and Friberg 1976) The rational of the analysis was to form factor discordant subsamples of twin pairs with concordant smoking habits Factors considered included drinking low physical activity frequent change of employer and occupational strain All of these factors showed in a multiple correlation analysis significant partial correlations with angina pectoris in the A series analysis In the B-series analysis however only drinking turned out to be significantly related to the symptom in qu stion

Finally in the Floderus (1974) study angina pectoris was related to another disease entity nervous diseases and a series of background variables indicating psycho-social strains (cf section 4 4) It was found that angina pectoris in males was 1 5 times and in females 2 times more prevalent among those who complained of nervous disease High ratios were also found for almost all of the psycho-social items For example angina pectoris was 1 5-1 7 times as common among those who had financial problems and 2 3 times as common among those who were not able to set aside work Further marriage difficulti s gave ratios of 1 5-1 9 shortage of time 1 4 restlessness 2 0 and sleeping difficulties 1 9 By studying smokers and nonsmokers separately only minor differences were found between the groups in regard to the risk ratio for angina pertoris and if anything the ratios were higher among nonsmokers However several of the psycho-social items were related to smoking On the basis of B-series analysis on item discordant monozygotic and dizygotic pairs Floderus concludes that the psycho-social discord items were found to discriminate subjects with respect to angina pectoris also when the influences of genetic and

Table 7 6 Continuation

	Born	Non-smokers	Cigarettes only <7	8-15	>16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Longlasting illness								
Males	1956-58	9 5	0 6	1 1	0 0	2 6	0 0	1 1
	1946-55	11 4	0 8	1 0	1 3	1 1	1 2	1 1
	1926-45	16 5	1 2	1 2	1 2	1 3	1 0	1 2
Females	1956-58	7 9	1 6	2 4	(3 2)[1]	-		1 7
	1946-55	10 4	0 9	1 1	1 8			1 2
	1926-45	15 9	1 1	1 2	1 6			1 4
Sick leave > 3 months in row								
Males	1956-58	0 9	3 3	1 7	0 0	4 2	0 0	1 1
	1946-55	4 4	1 3	1 7	2 2	1 7	1 2	1 6
	1926-45	12 2	1 1	1 6	1 6	1 8	1 2	1 2
Females	1956-58	0 4	2 5	0 0	(20 8)			0 0
	1946-5	3 3	1 5	2 1	3 7			1 4
	1926-45	11 0	1 2	1 6	2 4			1 5

7 2 4 Selected disease entities other than respiratory and cardiovascular

In the two twin registrie in Sweden some questions were also asked about morbidity other than respiratory and cardiovascular

The questionnaire mailed to the new twin registry asked for information about series of symptoms as well as long-lasting illnes and sick leave for more than and equal to 3 months in a row Table 7 6 presents data in the A-series fashion

It appears from the table that every item listed shows a significant hypermorbidity in one or more of the subgroups The tabl also contains individual who were between 15 and 17 years of age at time of observation and several diseases such as stomach disorders back disorder impaired hearing and long-lasting illness were lready ignificantly increased among such subjects who smoked les than 8 cigarettes day Stomach and back disorders are learly related to number of cigarettes smoked even in this youngest age group

Without exception all items show dose related hypermorbidity ratios in the older age groups for both mal and females Cigarette and pipe smoking and pipe only smoking also show significant excess morbidity for most of the symptoms in the youngest age group as well though the numbers are not large enough to make the atios significant.

Table 7 6 Selected Data on Diseases by Sex and Age; Age-adjusted Morbidity Ratios in Smoking Groups in Relation to Prevalence Rates among Nonsmokers; New Swedish Twin Registry A-series[1]

	Born	Non-smokers	Cigarettes only ≤7	Cigarettes only 8-15	Cigarettes only ≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Stomach disorders								
Males	1956-58	4 1	1 1	1 9	(3 5)	2 8	(1 4)	1 4
	1946-55	9 2	1 5	1 7	2 3	2 0	1 5	1 3
	1926-45	12 2	1 7	1 7	2 3	2 2	1 6	1 7
Females	1956-58	7 7	1 6	2 7	(2 2)	-	-	1 5
	1946-55	17 2	1 3	1 6	2 5	-	-	1 4
	1926-45	19 4	1 1	1 6	2 1		-	1 3
Back disorders								
Males	1956-58	4 1	2 9	3 0	(10 5)	4 7	(4 1)	2 4
	1946-55	9 3	1 3	1 8	2 5	1 9	1 4	1 4
	1926-45	16 7	1 2	1 3	1 4	1 5	1 4	1 1
Females	1956-58	4 4	2 5	3 6	(1 9)	-	-	2 2
	1946-55	6 9	1 3	2 0	3 2		-	1 3
	1926-45	13 4	1 1	1 5	1 7			1 4
Decreased hearing								
Males	1956 58	4 1	0 4	2 2	0 0	1 9	(1 4)	2 1
	1946-55	6 2	1 7	1 3	1 2	1 5	1 6	0 9
	1926-45	10 2	1 2	1 3	1 2	1 4	1 5	1 4
Females	1956-58	2 6	2 8	3 3	(6 4)			3 3
	1946-55	3 1	0 9	1 4	2 7	-		1 1
	1926-45	4 8	1 2	1 0	1 6			1 4
Migrain								
Males	1956-58	1 3	2 3	1 2	0 0	1 0	0 0	0 8
	1946-55	1 2	1 7	1 8	2 9	1 6	0 7	1 0
	1926-45	2 8	0 7	1 3	1 5	1 5	1 3	0 9
Females	1956-58	1 4	1 7	1 4	(5 9)			0 7
	1946-55	4 4	1 2	1 3	2 1			1 3
	1926-45	8 3	0 7	1 0	1 4			1 2
Asthma								
Males	1956-58	18 2	0 9	0 9	(1 6)	1 1	(1 5)	0 9
	1946-55	14 1	1 0	0 9	1 1	1 1	1 1	1 3
	1926-45	14 2	0 8	0 9	0 8	1 0	0 9	1 0
Females	1956-58	17 9	1 1	1 4	(3 3)		-	1 3
	1946-55	17 1	1 0	1 1	1 4			1 2
	1926-45	17 1	1 0	1 0	1 3			1 2

1) For numbers at risk see table 6 1

continuation

Table 7 6 Continuation

	Born	Non-smokers	Cigarettes only			Cigarettes and pipe	Pipe only	Former smokers
			<7	8-15	≥16			
		Prevalence Rate	Ratio			Ratio		
Longlasting illness								
Males	1956-58	9 5	0 6	1 1	0 0	2 6	0 0	1 1
	1946-55	11 4	0 8	1 0	1 3	1 1	1 2	1 1
	1926-45	16 5	1 2	1 2	1 2	1 3	1 0	1 2
Femal	1956-58	7 9	1 6	2 4	(3 2)			1 7
	1946-55	10 4	0 9	1 1	1 8		-	1 2
	1926-45	15 9	1 1	1 2	1 6		-	1 4
Sick leave > 3 months in row								
Males	1956-58	0 9	3 3	1 7	0 0	4 2	0 0	1 1
	1946-55	4 4	1 3	1 7	2 2	1 7	1 2	1 6
	1926-45	12 3	1 1	1 6	1 6	1 8	1 2	1 2
Femal	1956-58	0 4	2 5	0 0	(20 8)			0 0
	1946-55	3 3	1 5	2 1	3 7		-	1 4
	1926-45	11 0	1 2	1 6	2 4			1 5

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In the two twin registri in Sweden some questions were also asked about morbidity other than respiratory and cardiovascular

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It appears from the table that every item listed shows a significant hypermorbidity in one more of the subgroups The table also contains individuals who were between 15 and 17 years of age t time of observation and several diseases such as tomach disorders back disorders impaired hearing and long-lasting illness were lready significantly increased among such subjects who smoked less than 8 cigarettes a day Stomach and back disorders are learly rel ted to number of cigarettes smoked even in this youngest age group

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	Born	Non-smokers	Cigarettes only ≤7	Cigarettes only 8-15	Cigarettes only ≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Stomach disorders								
Males	1956-58	4 1	1 1	1 9	(3 5)	2 8	(1 4)	1 4
	1946-55	9 2	1 5	1 7	2 3	2 0	1 5	1 3
	1926-45	12 2	1 7	1 7	2 3	2 2	1 6	1 7
Females	1956-58	7 7	1 6	2 7	(2 2)	-	-	1 5
	1946-55	17 2	1 3	1 6	2 5		-	1 4
	1926-45	19 4	1 1	1 6	2 1	-	-	1 3
Back disorders								
Males	1956-58	4 1	2 9	3 0	(10 5)	4 7	(4 1)	2 4
	1946-55	9 3	1 3	1 8	2 5	1 9	1 4	1 4
	1926-45	16 7	1 2	1 3	1 4	1 5	1 4	1 1
Females	1956-58	4 4	2 5	3 6	(1 9)	-		2 2
	1946-55	6 9	1 3	2 0	3 2			1 3
	1926-45	13 4	1 1	1 5	1 7		-	1 4
Decreased hearing								
Males	1956-58	4 1	0 4	2 2	0 0	1 9	(1 4)	2 1
	1946-55	6 2	1 7	1 3	1 2	1 5	1 6	0 9
	1926-45	10 2	1 2	1 3	1 2	1 4	1 5	1 4
Females	1956-58	2 6	2 8	3 3	(6 4)		-	3 3
	1946-55	3 1	0 9	1 4	2 7	-	-	1 1
	1926-45	4 8	1 2	1 0	1 6	-		1 4
Migrain								
Males	1956-58	1 3	2 3	1 2	0 0	1 0	0 0	0 8
	1946-55	1 2	1 7	1 8	2 9	1 6	0 7	1 0
	1926-45	2 8	0 7	1 3	1 5	1 5	1 3	0 9
Females	1956-58	1 4	1 7	1 4	(5 9)			0 7
	1946-55	4 4	1 2	1 3	2 1			1 3
	1926-45	8 3	0 7	1 0	1 4			1 2
Asthma								
Males	1956-58	18 2	0 9	0 9	(1 6)	1 1	(1 5)	0 9
	1946-55	14 1	1 0	0 9	1 1	1 1	1 1	1 3
	1926-45	14 2	0 8	0 9	0 8	1 0	0 9	1 0
Females	1956-58	17 9	1 1	1 4	(3 3)	-		1 3
	1946-55	17 1	1 0	1 1	1 4		-	1 2
	1926-45	17 1	1 0	1 0	1 3			1 2

1) For numbers at risk see table 6 1

continuation

Tabl 7 6 Continuation

	Born	Non-smoker	Cigarette only ≤7	8–15	≥16	Cigarettes and pipe	Pipe only	Former smokers
		Prevalence Rate	Ratio			Ratio		
Longlasting illness								
Males	1956–58	9 5	0 6	1 1	0 0	2 6	0 0	1 1
	1946–55	11 4	0 8	1 0	1 3	1 1	1 2	1 1
	1926–45	16 5	1 2	1 2	1 2	1 3	1 0	1 2
Females	1956–58	7 9	1 6	2 4	(3 2)	-		1 7
	1946–55	10 4	0 9	1 1	1 8*			1 2
	1926–45	15 9	1 1	1 2	1 6			1 4
Sick leave 3 months in row								
Males	1956–58	0 9	3 3	1 7	0 0	4 2	0 0	1 1
	1946–55	4 4	1 3	1 7	2 2	1 7	1 2	1 6
	1926–45	12 2	1 1	1 6	1 6	1 8	1 2	1 2
Females	1956–58	0 4	2 5	0 0	(20 8)			0 0
	1946–55	3 3	1 5	2 1	3 7			1 4
	1926–45	11 0	1 2	1 6	2 4			1 5

7 2 4 Selected di ease entities other than respiratory and cardiovascular

In the two twin registries in Sweden some questions were lso asked about morbidity other than respiratory and cardiovascular

The questionnaire mailed to the new twin registry asked for information about series f symptoms as well as long-lasting illnes and sick leave for more than and equal to 3 months in a row Tabl 7 6 presents data in the A-serie fashion

It appears from the tabl that every item listed shows a significant hypermorbidity in one o more of the subgroups The table also contains individuals who were between 15 and 17 years of age t time of observation and several diseases such stomach disorders back disorders impaired hearing and long-lasting illness were already significantly increased among such subjects who smoked less than 8 cigarette day Stomach and back disorders are learly related to number of cigarettes smoked even in thi youngest age group

Without exception all items show dose related hypermorbidity atios in the older age groups f both males and females Cigarette and pipe smoking and pipe only smoking lso show significant excess morbidity for most of the symptoms in the youngest age group as well though the numbers are not large enough to make the ratios significant.

Table 7 6 Selected Data on Diseases by Sex and Age; Age-adjusted Morbidity Ratios in Smoking Groups in Relation to Prevalence Rates among Nonsmokers; New Swedish Twin Registry A-series[1]

	Born	Non smokers	Cigarettes only			Cigarettes and pipe	Pipe only	Former smokers
			≤7	8-15	≥16			
		Prevalence Rate		Ratio			Ratio	
Stomach disorders								
Males	1956-58	4 1	1 1	1 9	(3 5)	2 8	(1 4)	1 4
	1946-55	9 2	1 5	1 7	2 3	2 0	1 5	1 3
	1926-45	12 2	1 7	1 7	2 3	2 2	1 6	1 7
Females	1956-58	7 7	1 6	2 7	(2 2)	-	-	1 5
	1946-55	17 2	1 3	1 6	2 5			1 4
	1926-45	19 4	1 1	1 6	2 1	-		1 3
Back disorders								
Males	1956-58	4 1	2 9	3 0	(10 5)	4 7	(4 1)	2 4
	1946-55	9 3	1 3	1 8	2 5	1 9	1 4	1 4
	1926-45	16 7	1 2	1 3	1 4	1 5	1 4	1 1
Females	1956-58	4 4	2 5	3 6	(1 9)	-		2 2
	1946-55	6 9	1 3	2 0	3 2	-		1 3
	1926-45	13 4	1 1	1 5	1 7		-	1 4
Decreased hearing								
Males	1956 58	4 1	0 4	2 2	0 0	1 9	(1 4)	2 1
	1946-55	6 2	1 7	1 3	1 2	1 5	1 6	0 9
	1926-45	10 2	1 2	1 3	1 2	1 4	1 5	1 4
Females	1956-58	2 6	2 8	3 3	(6 4)			3 3
	1946-55	3 1	0 9	1 4	2 7		-	1 1
	1926-45	4 8	1 2	1 0	1 6			1 4
Migrain								
Males	1956-58	1 3	2 3	1 2	0 0	1 0	0 0	0 8
	1946-55	1 2	1 7	1 8	2 9	1 6	0 7	1 0
	1926-45	2 8	0 7	1 3	1 5	1 5	1 3	0 9
Females	1956-58	1 4	1 7	1 4	(5 9)	-		0 7
	1946-55	4 4	1 2	1 3	2 1			1 3
	1926-45	8 3	0 7	1 0	1 4			1 2
Asthma								
Male	1956-58	18 2	0 9	0 9	(1 6)	1 1	(1 5)	0 9
	1946-55	14 1	1 0	0 9	1 1	1 1	1 1	1 3
	1926-45	14 2	0 8	0 9	0 8	1 0	0 9	1 0
Female	1956-58	17 9	1 1	1 4	(3 3)			1 3
	1946-55	17 1	1 0	1 1	1 4			1 2
	1926-45	17 1	1 0	1 0	1 3		-	1 2

1) For numbers at risk see table 6 1

continuation

Tabl 7 8 Selected Data on Diseases; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-Twin; New Swedish Twin Registry MET-series

		Non-Smokers	Present Cigarette Smokers	All Present Smokers	Former Smokers
No t risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Stomach disorders	MZ	0 97	1 33	1 35	1 42
	DZ	0 94	1 17	1 15	1 06
Back disorders	MZ	0 86	1 35	1 24	1 41
	DZ	0 96	1 06	1 05	0 90
Decreased hearing	MZ	1 02	1 20	1 24	1 01
	DZ	0 99	1 18	1 04	1 00
Migrain	MZ	0 90	2 64	2 05	0 76
	DZ	0 91	1 10	1 14	1 19
Asthma	MZ	0 97	1 24	1 20	1 32
	DZ	1 01	0 87	0 90	1 07
Longlasting illnes	MZ	0 99	1 02	1 09	1 54
	DZ	0 99	0 93	0 96	1 27
Sick leave 3	MZ	0 92	1 55	1 53	0 96
months in row	DZ	1 00	1 03	1 03	1 24

Table 7 7 Selected Data on Diseases; *Sex and Age Standardized Ratios of* Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-Twin; New Swedish Twin Registry NET-series

		Non-Smokers	Present Cigarette Smokers	All Present Smokers	Former Smokers
No at risk	MZ	1881	340	423	270
	DZ	2236	1010	1307	544
Cough	MZ	0 88	2 71	1 72	1 28
	DZ	1 00	1 11	1 07	0 78
Pains in the chest	MZ	0 97	1 62	1 32	1 24
	DZ	0 94	1 04	0 95	1 34
Shortness of breath	MZ	0 94	1 25	1 24	1 24
	DZ	0 93	1 06	1 07	1 05

Former smokers also display increased hypermorbidity ratios for all items except possibly migraine The ratios are of about the same order of magnitude as in the group of present cigarette smokers smoking 7 cigarettes or less a day

7 2 5 Symptoms among nonsmoking partners of smoking co-twins

In section 6 3 it was shown that several items such as drinking and indications of psycho-social discord were more prevalent among nonsmoking partners of presently smoking co-twins than could be expected from prevalence rates in the total group of nonsmokers This section will deal with the same type of analysis with respect to the symptoms reported from the New Registry in foregoing sections

Table 7 7 displays sex- and age standardized prevalence ratios of cough pains in the chest and shortness of breath among nonsmoking partners grouped according to the smoking status of their co-twins It appears that all three symptoms show significantly increased ratios in the monozygotic twins with presently smoking partners This effect is however not seen among dizygotes except for pains in the chest in twins with formerly smoking partners

Table 7 8 comprises data on other symptoms corresponding to the data in table 7 6 It is again seen that all items show with one single exception hypermorbidity ratios that are higher and very often significantly so among the monozygotes Among the highest ratios are migraine and sick leave more than and equal to 3 months in a row

Table 7 8 Selected Data on Diseases; Sex and Age Standardized Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-Twin; New Swedish Twin Registry NET-series

		Non-Smokers	Present Cigarette Smoker	All Present Smokers	Former Smokers
No t risk	MZ	1081	340	423	270
	DZ	2236	1010	1307	544
Stomach disorders	MZ	0 97	1 33	1 35	1 42
	DZ	0 94	1 17	1 15	1 06
Back disorders	MZ	0 86	1.35	1 24	1 41
	DZ	0 96	1 06	1 05	0 90
Decreased hearing	MZ	1 02	1 20	1 24	1 01
	DZ	0 99	1 18	1 04	1 00
Migrain	MZ	0 90	2 64	2 0	0 76
	DZ	0 91	1 10	1 14	1 19
Asthma	MZ	0 97	1 24	1 20	1 32
	DZ	1 01	0 87	0 90	1 07
Longlasting illness	MZ	0 99	1 02	1 09	1 54
	DZ	0 99	0 93	0 96	1 27
Sick leave >3 months in row	MZ	0 92	1 55	1 53	0 96
	DZ	1 00	1 03	1 03	1 24

7 3 Twin Studies: Mortality

(in collaboration with Ulf de Faire[1] MD and Ulla Lorich[2] BA)

7 3 1 Introductory remarks

The follow-up of mortality in the old Swedish twin registry has been going on since the start of the registry in 1961 The first results were reported in 1970 and a second publication appeared in 1973 The last mentioned report included all deaths that had occurred before July 1 1972 The following tables will present data on deaths accumulated up to and including June 1975 The presentation by and large will follow the main principles laid down in the 1973 report Thus A series analyses are first presented giving accumulated rate of deaths in nonsmokers and hypermortality ratios by age and sex in different smoking categories All prevalence rates and accordingly the hypermortality ratios are age adjusted on the basis of 5-year age intervals The outcome of the A analyses will not be commented upon if they do not notably deviate from what is generally found in studies on unrelated smokers and nonsmokers

As in the earlier reports the B-series analyses focus on the concept of first deaths This is necessary because of the longitudinal approach: the working hypothesis is that a smoker in a smoking discordant pair will die on an average before his nonsmoking partner Thus for pairs with two deceased twins only the first deceased twin is included in the subsequent Analysis However in order not to suppress information that may interest the reader the second deaths are included in the tables as subscripts

Table 7 9 Age-adjusted Mortality Rates among Nonsmokers and Mortality Ratios by Sex Age and Smoking Groups; Old Swedish Twin Registry A-series

	Born	Non smokers	Present Smokers ≤10 cgts	Present Smokers >10 cgts	Present Smokers Cigar/ pipe	Former Smokers ≤10 cgts	Former Smokers >10 cgts	Former Smokers Cigar/ pipe
No at Risk								
Males	1911-25	1707	1249	793	890	384	239	157
	1901-10	881	537	231	472	212	99	184
Females	1911-25	4770	1111	322	-	286	44	-
	1901-10	2824	285	75	-	76	9	
		Rate		Ratios			Ratios	
Mortality								
Males	1911-25	4 7	1 7	2 0	1 3	1 1	1 6	1 0
	1901-10	16 3	1 2	2 2	1 3	1 1	1 8	0 8
Females	1911-25	3 6	1 5	2 0	-	1 3	(2 2)	
	1901-10	13 2	1 1	1 8	-	0 9	(0 6)	

1) The Department of Medicine of the Karolinska Institute at the Serafimer Hospital Stockholm

2) The Department of Environmental Hygiene the Karolinska Institute Stockholm

The detailed classification of smoking discordance presented in Chapter 4 is the same as in previous reports yielding two groups for analyses One group contains nonsmokers versus cigarette smokers[1] The other group consists of the same pair as the before mentioned group plus a number f pairs where both members smoke cigarettes but are discordant in regard to quantity The last mentioned pooled groups are designated as "pooled low group versus "pooled high group[2]

The B-series tables include present smoker and former smokers (top of table) as well as present smokers only (bottom of table)

7 3 2 Gross mortality

Age adjusted mortality rates are presented in the A series fashion in table 7 9 by sex age and smoking groups

As the first step in the B-series analyses mortality data are given as incidences during three succes ive 5-year intervals since the beginning of the study in 1961 Table 7 10 shows the incidence by sex zygosity and year of death in the pooled low and pooled high groups Only the total cohort i presented as further breakdown would render the numbers too low

Table 7 10 Mortality by Sex Zygosity and Year of Death and the Total Cohort f Smoking Discordance Groups; Old Swedish Twin Registry Age Group 1901 25 First Deaths Only B-series

	Year f Death	DIZYGOTES Person Year of Observation	Pooled Low Group	Pooled High Group	MONOZYGOTES Person Years of Observation	Pooled Low Group	Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1961-65	3502	9	16	1224	8	4
	1966-70	3318	17	30	1129	10	10
	1971 75[3]	2749	28	36	933	6	13
Females	1961-65	3882	7	12	1622	3	4
	1966-70	3737	18	22	1585	5	5
	1971 75[3]	3172	19	26	1343	14	17
PRESENT SMOKERS ONLY							
Males	1961-65	2416	6	7	831	6	3
	1966-70	2299	13	22	773	6	7
	1971 75[3]	1896	18	27	629	3	9
Females	1961-65	3084	6	11	1251	2	1
	1966-70	2968	15	16	1230	3	5
	1971 75[3]	2515	17	21	1037	12	16

1) The igarette smoker may also smoke pipe and/or cigar
2) The "high smoker may also smok pipe and/ cigars
3) June 1975

Table 7 11 Mortality[1] by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B series

	Born	DIZYGOTES No of Pairs	DIZYGOTES Non-smokers	DIZYGOTES Smokers	MONOZYGOTES No of Pairs	MONOZYGOTES Non-smokers	MONOZYGOTES Smokers
PRESENT AND FORMER SMOKERS							
Nonsmokers versus Smokers							
Males	1911-25	364	18	21_2	115	3_1	8
	1901-10	157	19_5	34_1	46	7	7_4
	1901-25	521	37_5	55_3	161	10_1	15_4
Females	1911-25	510	18_3	29_2	213	12	13_2
	1901-10	174	25_3	23_1	59	6_1	9_1
	1901-25	684	43_6	52_3	272	18_1	22_3
Pooled Low versus Pooled High Group		No of Pairs	Low	High	No of Pairs	Low	High
Males	1911-25	501	26_2	34_2	177	9_1	14
	1901-10	205	28_6	48_4	69	15_3	13_8
	1901-25	706	54_8	82_6	246	24_4	27_8
Females	1911-25	588	18_3	31_2	262	15	17_2
	1901-10	193	26_3	29_1	64	7_1	9_1
	1901-25	781	44_6	60_3	326	22_1	26_3
PRESENT SMOKERS ONLY							
Nonsmokers versus Smokers							
Males	1911-25	274	13	19_1	77	2_1	7
	1901-10	101	14_5	21_1	34	5	4_3
	1901-25	375	27_5	40_2	111	7_1	11_3
Females	1911-25	421	16_3	23_2	167	10	11_1
	1901-10	131	21_2	18_1	48	5_1	7_1
	1901-25	552	37_5	41_3	215	15_1	18_2
Pooled Low versus Pooled High Group		No of Pairs	Low	High	No of Pairs	Low	High
Males	1911-25	356	16_1	28_1	123	6_1	12
	1901-10	130	21_5	28_4	44	9_2	7_5
	1901-25	486	37_6	56_5	167	15_3	19_5
Females	1911-25	477	16_3	25_2	199	11	15_1
	1901-10	144	22_2	23_1	52	6_1	7_1
	1901-25	621	38_5	48_3	251	17_1	22_2

1) *In pairs in which both members have died* first deceased member has been recorded in proper smoking status group while partner is shown in subscript number Total number of deaths can be obtained by adding subscript figures to main *figures* *As an example* among 364 nonsmoking smoking dizygotic male twin pairs belonging to 1911 25 age group 18 first deaths have occurred among nonsmokers and 21 first deaths among smokers Two more deaths were *found among* smokers but this occurred

It is apparent from tabl 7 10 that the incidence as far as the dizygotes are concerned has been consistently higher for the pooled high group than for the pooled low group throughout all three 5-year periods This is true for both males and females and also when former smokers are excluded. In the monozygotic groups the numbers are low No consistent difference can be noted between the pooled low group and the pooled high group during the first 10 years of observ tion During the last 5 year however higher although not ignificantly higher incidence has been noted in the pooled high group for both sexes When males and females are taken together the monozygotic incidence atios during this last period of observ tion ar 1 5 for present and former smokers and 1 7 for present smokers only These ratios are about the same as those for the dizygotes which are 1 3 and 1 4 espectively

In tabl 7 11 the total accumulated mortality up to and including June 1975 i presented by sex age and zygosity in the two smoking discord ance groups The following comments relate primarily to the total cohort born 1901 1925 ince the numbers are low when the age groups are taken separately

Among the dizygotes the diff rences between nonsmokers and smokers and between the two pooled exposure groups are apparent for both males and females For the total cohort of present and former smokers born 1901 1925 the hypermortality ratios are about 1 5 for males and about 1 2 1 4 for females These ratios are significant for males The monozygoti groups also show excess deaths among the exposed The numbers are low however and the observed differences do not reach statistical signifi cance About the same exce is seen irrespective of whether former smokers are ex luded o not The hypermortality in th exposed mal monozygotes is found mainly in the younger age-group

7 3 3 Selected cause-specific mortality

Just as in the earlier reports from the Swedish Twin Registry cause-specific mortality ha been been classified for the diagnoses coronary heart disease cardiovascular disease cance of the lung othe forms of cancer suicides and accidents These entities together with other causes are presented in the A-series fashion in table 7 12 page 98 for males and females respectively The results are not age adjusted

Coronary heart disease In the B-serie analyses (table 7 13 page 99) because f small numbers only the pooled low group and the pooled high group are shown In the dizygoti series both males and females show mortality rates that ar about twice as high in the pooled high group as compared to the pooled low group namely 25 as against 13 in males and 11 as against 5 in the females Among the mal monozygotes 10 cases ar observed in the high group versus 8 in the low group If former smokers are excluded mal dizygotes show 18 deaths in the pooled high group and 7 in the pooled low group Corresponding numbers for the monozygotes are 6 against 6 For females the numbers are 8 5 and 3 1 respectively

Cance of the lung In the B-series analysis (tabl 7 14 page 99) among the dizygotic males f rmer smokers included there were 9 lung cance cases in the pooled high group as against 2 cases in the pooled low group Among the mal monozygotes two cases occurred in the pooled high group and one case in the pooled low group (cf section 8 3 3) Of the two cases in the dizygoti pooled low group one has occurred in a former smoker

Table 7 12 Mortality Rates Among Nonsmokers and Mortality Ratios[1] from Selected Causes by Sex Age and Smoking Groups; Old Swedish Twin Registr A-series[2]

	Born	Non-smokers	Present Smokers <10 cgts	Present Smokers >10 cgts	Present Smokers Cigar/ pipe	Former Smokers <10 cgts	Former Smokers >10 cgts	Former Smokers Cigar pipe
		Prevalence Rate	Ratios			Ratios		
Coronary Heart Disease								
Males	1911-25	1 1	2 1*	2 6	1 5	1 5	1 2	1 7
	1901-10	3 7	2 0	2 9*	2 5	1 8	3 8	1 5
Females	1911-25	0 3	1 0	1 0	-	1 3	(7 7)	
	1901-10	2 7	2 2	1 0	-	1 4	-	
Cerebrovascular Disease								
Males	1911-25	0 3	0 7	1 7	0 7	1 0	-	
	1901-10	1 2	1 6	1 4	2 1	1 2	0 8	1 3
Females	1911-25	0 3	1 3	5 3*	-	1 3	-	
	1901-10	1 7	0 6	0 8	-	-	-	
Cancer of the Lung								
Males	1911-25	0 06	5 5	12 9	7 7	-	-	21 7
	1901-10	0 23	6 6	24 8	5 6	2 1	4 4	-
Females	1911-25	0 04	-	7 4	-	-	-	-
	1901-10	0 11	6 6	12 6	-	-	-	-
Other Cancers								
Males	1911-25	1 2	0 5	1 3	1 1	1 5	1 8	0 5
	1901-10	3 6	1 2	1 3	1 2	1 8	1 4	0 6
Females	1911-25	1 8	1 3	1 1	-	1 1	(1 3)	-
	1901-10	4 5	0 7	1 8	-	1 8	-	
Suicides								
Males	1911-25	0 4	2 5	2 8	1 8	0 8	2 0	-
	1901-10	0 7	0 3	1 9	0 9	0 7	1 4	
Females	1911-25	0 2	2 0	8 0	-	-	(11 5)	-
	1901-10	0 2	-	-	-	-	-	-
Accidents								
Males	1911-25	0 5	1 4	2 6	1 2	0 6	2 6	
	1901-10	1 5	0 4	1 7	0 7	0 6	1 3	-
Females	1911-25	0 3	0 7	2 0	-			-
	1901-10	0 5	1 4	-	-	-	(22 2)	-
Other Causes								
Males	1911-25	1 2	1 9	0 9	0 8	1 1	1 8	1 1
	1901-10	5 3	0 8	1 5	0 6	0 5	1 0	0 8
Females	1911-25	0 8	1 5	0 4	-	1 4	-	
	1901-10	3 5	0 7	2 3	-	-	-	-

1) Not adjusted for age
2) For numbers at risk see table 7 9

Table 7 13 Mortality[1] from Coronary Heart Disease by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No of Pairs	Pooled Low Group	Pooled High Group	MONOZYGOTES No of Pairs	Pooled Low Group	Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911 25	501	7	9_{1}	177	2	3
	1901 10	205	6_{3}	16_{2}	69	6_{2}	7_{4}
	1901 25	706	13_{3}	25_{3}	246	8_{2}	10_{4}
Females	1911 25	588	0	0	262	1	0
	1901 10	193	5_{1}	11_{1}	64	0	3_{1}
	1901 25	781	5_{1}	11_{1}	326	1	3_{1}
PRESENT SMOKERS ONLY							
Males	1911 25	356	2	8_{1}	123	2	3
	1901 10	130	5_{3}	10_{2}	44	4_{2}	3_{2}
	1901 25	486	7_{3}	18_{3}	167	6_{2}	6_{2}
Females	1911 25	477	0	0	199	1	0
	1901 10	144	5	6_{1}	52	0	3_{1}
	1901 25	621	5	8_{1}	251	1	3_{1}

Tabl 7 14 Mortality[1] from Cancer of the Lung by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No of Pairs	Pooled Low Group	Pooled High Group	MONOZYGOTES No of Pairs	Pooled Low Group	Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911 25	501	0	2	177	0	0
	1901 10	205	2	7	69	1	2
	1901 25	706	2	9	246	1	2
Femal	1911 25	588	0	0	262	0	0
	1901 10	193	0	1	64	1	0
	1901 25	781	0	1	326	1	0
PRESENT SMOKERS ONLY							
Males	1911 25	356	0	2	123	0	0
	1901 10	130	1	7	44	1	2
	1901 25	486	1	9	167	1	2
Females	1911 25	477	0	0	199	0	0
	1901 10	144	0	1	52	1	0
	1901 25	621	0	1	251	1	0

1) See footnote to tabl 7 11

Table 7 12 Mortality Rates Among Nonsmokers and Mortality Ratios[1] from Selected Causes by Sex Age and Smoking Groups; Old Swedish Twin Registry A-series[2]

	Born	Non-smokers	Present Smokers <10 cgts	Present Smokers >10 cgts	Present Smokers Cigar/pipe	Former Smokers <10 cgts	Former Smokers >10 cgts	Former Smokers Cigar/pipe
		Prevalence Rate	Ratios			Ratios		
Coronary Heart Disease								
Males	1911-25	1 1	2 1	2 6	1 5	1 5	1 2	1 7
	1901-10	3 7	2 0	2 9	2 5	1 8	3 8	1 5
Females	1911-25	0 3	1 0	1 0	-	1 3	(7 7)	
	1901-10	2 7	2 2	1 0	-	1 4	-	
Cerebrovascular Disease								
Males	1911-25	0 3	0 7	1 7	0 7	1 0	-	-
	1901-10	1 2	1 6	1 4	2 1	1 2	0 8	1 3
Females	1911-25	0 3	1 3	5 3	-	1 3	-	
	1901-10	1 7	0 6	0 8	-	-	-	
Cancer of the Lung								
Males	1911-25	0 06	5 5	12 9	7 7	-	-	21 7
	1901 10	0 23	6 6*	24 8	5 6	2 1	4 4	-
Females	1911-25	0 04	-	7 4	-	-	-	
	1901-10	0 11	6 6	12 6	-	-	-	-
Other Cancers								
Males	1911-25	1 2	0 5	1 3	1 1	1 5	1 8	0 5
	1901-10	3 6	1 2	1 3	1 2	1 8	1 4	0 6
Females	1911-25	1 8	1 3	1 1	-	1 1	(1 3)	-
	1901-10	4 5	0 7	1 8		1 8	-	
Suicides								
Males	1911-25	0 4	2 5	2 8	1 8	0 8	2 0	-
	1901-10	0 7	0 3	1 9	0 9	0 7	1 4	-
Females	1911-25	0 2	2 0	8 0	-	-	(11 5)	-
	1901-10	0 2	-	-	-	-	-	-
Accidents								
Males	1911-25	0 5	1 4	2 6	1 2	0 6	2 6	
	1901-10	1 5	0 4	1 7	0 7	0 6	1 3	
Females	1911-25	0 3	0 7	2 0	-	-		
	1901-10	0 5	1 4	-	-	-	(22 2)	-
Other Causes								
Males	1911-25	1	1 9	0 9	0 8	1 1	1 8	1 1
	1901-10	5 3	0 8	1 5	0 6	0 5	1 0	0 8
Females	1911-25	0 8	1 5	0 4	-	1 4	-	-
	1901-10	3 5	0 7	2 3	-	-	-	-

1) Not adjusted for age
2) For numbers at risk see table 7 9

Table 7 13 Mortality[1] from Coronary Heart Disease by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No of Pair	DIZYGOTES Pooled Low Group	DIZYGOTES Pooled High Group	MONOZYGOTES No of Pair	MONOZYGOTES Pooled Low Group	MONOZYGOTES Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911 25	501	7	9_1	177	2	3
	1901 10	205	6_3	16^1_2	69	6_2	7_4
	1901 25	706	13^3_3	25^2_3	246	8^2_2	10^4_4
Females	1911 25	588	0	0	262	1	0
	1901 10	193	5_1	11_1	64	0	3_1
	1901 25	781	5^1_1	11^1_1	326	1	3^1_1
PRESENT SMOKERS ONLY							
Males	1911 25	356	2	8_1	123	2	3
	1901 10	130	5_3	10^1_2	44	4_2	3_2
	1901 25	486	7^3_3	18^2_3	167	6^2_2	6^2_2
Females	1911 25	477	0	0	199	1	0
	1901 10	144	5	8_1	52	0	3_1
	1901 25	621	5	8^1_1	251	1	3^1_1

Tabl 7 14 Mortality[1] from Cancer of the Lung by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No f Pairs	DIZYGOTES Pooled Low Group	DIZYGOTES Pooled High Group	MONOZYGOTES No of Pairs	MONOZYGOTES Pooled Low Group	MONOZYGOTES Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911 25	501	0	2	177	0	0
	1901 10	20	2	7	69	1	2
	1901 25	706	2	9	246	1	2
Females	1911 25	588	0	0	262	0	0
	1901 10	193	0	1	64	1	0
	1901 25	781	0	1	326	1	0
PRESENT SMOKERS ONLY							
Males	1911 25	356	0	2	123	0	0
	1901 10	130	1	7	44	1	2
	1901 25	486	1	9	167	1	2
Females	1911 25	477	0	0	199	0	0
	1901 10	144	0	1	52	1	0
	1901 25	621	0	1	251	1	0

1) See footnote to tabl 7 11

Table 7 12 Mortality Rates Among Nonsmokers and Mortality Ratios[1] fro Selected Causes by Sex Age and Smoking Groups; Old Swedish Twin Registr A-series[2]

	Born	Non-smokers	Present Smokers			Former Smokers		
			<10 cgts	>10 cgts	Cigar/ pipe	<10 cgts	>10 cgts	Ciga pipe
		Prevalence Rate		Ratios			Ratios	
Coronary Heart Disease								
Males	1911-25	1 1	2 1	2 6	1 5	1 5	1 2	1 7
	1901-10	3 7	2 0	2 9	2 5	1 8	3 8	1 5
Females	1911-25	0 3	1 0	1 0	-	1 3	(7 7)	
	1901-10	2 7	2 2	1 0	-	1 4	-	
Cerebrovascular Disease								
Males	1911-25	0 3	0 7	1 7	0 7	1 0	-	
	1901-10	1 2	1 6	1 4	2 1	1 2	0 8	1 3
Females	1911-25	0 3	1 3	5 3	-	1 3	-	
	1901-10	1 7	0 6	0 8	-	-	-	-
Cancer of the Lung								
Males	1911-25	0 06	5 5	12 9	7 7*	-	-	21 7
	1901-10	0 23	6 6	24 8	5 6	2 1	4 4	-
Females	1911-25	0 04	-	7 4	-	-	-	
	1901-10	0 11	6 6	12 6	-	-	-	-
Other Cancers								
Males	1911-25	1 2	0 5	1 3	1 1	1 5	1 8	0 5
	1901-10	3 6	1 2	1 3	1 2	1 8	1 4	0 6
Females	1911-25	1 8	1 3	1 1	-	1 1	(1 3)	-
	1901-10	4 5	0 7	1 8	-	1 8		-
Suicides								
Males	1911-25	0 4	2 5	2 8	1 8	0 8	2 0	-
	1901-10	0 7	0 3	1 9	0 9	0 7	1 4	
Females	1911-25	0 2	2 0	8 0	-	-	(11 5)	
	1901-10	0 2	-	-	-		-	
Accidents								
Males	1911-25	0 5	1 4	2 6	1 2	0 6	2 6	
	1901-10	1 5	0 4	1 7	0 7	0 6	1 3	
Females	1911-25	0 3	0 7	2 0	-	-	-	
	1901-10	0 5	1 4	-	-	-	(22 2)	-
Other Causes								
Males	1911-25	1 2	1 9	0 9	0 8	1 1	1 8	1 1
	1901-10	5 3	0 8	1 5	0 6	0 5	1 0	0 8
Females	1911-25	0 8	1 5	0 4	-	1 4	-	-
	1901-10	3 5	0 7	2 3	-	-	-	-

1) Not adjusted for age
2) For numbers at risk see table 7 9

Cancer other than that of the lung In the male dizygotic group the B-series analysis reveals a higher number of deaths in the pooled low group (table 7 15) The same tendency is not seen in the female group nor in the monozygotes or in the A-series where the picture is inconsistent. Exclusion of former smokers does not make the findings more clear

Suicides The A-series analysis (table 7 12 page 98) despite small numbers shows rates that significantly relate to smoking It is most apparent in the younger age group and is seen for both males and females Similar results are found in the B-series (table 7 16) For the total cohort of males and females taken together the dizygotes show 11 cases of suicides in the pooled high group as against 4 cases in the pooled low group Corresponding number for the monozygotes ar 6 cases versus 1 Only two cases of suicide occurred among former smokers

Accidents In the A-series a relation between accidents and smoking is seen mainly among male igarette smokers both former and present and in both age groups In the B-series analysis (table 7 17) th numbers are very low but do not as far as the dizygotes are concerned contradict the findings in the A-series Data from present smokers only does not change the picture

Table 7 17   Mortality[1] from Accidents by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

		DIZYGOTES			MONOZYGOTES		
	Born	No of Pairs	Pooled Low Group	Pooled High Group	No of Pairs	Pooled Low Group	Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911 25	501	5	4	177	2	3
	1901 10	205	0	4	69	1	0[1]
	1901 25	706	5	8	246	3	3[1]
Females	1911 25	588	2	3	262	2	0
	1901 10	193	0	2	64	0	1
	1901 25	781	2	5	326	2	1
PRESENT SMOKERS ONLY							
Mal	1911 25	356	4	3	123	1	2
	1901 10	130	0	3	44	1	0
	1901–25	486	4	6	167	2	2
Femal	1911 25	477	2	3	199	2	0
	1901 10	144	0	1	52	0	1
	1901 25	621	2	4	251	2	1

1) See footnote to table 7 11

Table 7 15 Mortality[1] from Cancer Other than from the Lung by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No of Pairs	DIZYGOTES Pooled Low Group	DIZYGOTES Pooled High Group	MONOZYGOTES No of Pairs	MONOZYGOTES Pooled Low Group	MONOZYGOTES Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911-25	501	8	3_1	177	0	1
	1901-10	205	10_1	6^1_1	69	1_1	3
	1901-25	706	18^1_1	9^1_2	246	1^1_1	4
Females	1911-25	588	7_3	12_1	262	9	8_1
	1901-10	193	13^3_1	8^1	64	2	3^1
	1901-25	781	20^1_4	20_1	326	11	11_1
PRESENT SMOKERS ONLY							
Males	1911-25	356	5	2	123	0	0
	1901-10	130	6_1	0_1	44	1	2
	1901-25	486	11^1_1	2^1_1	167	1	2
Females	1911-25	477	6_3	8_1	199	6	8
	1901-10	144	12^3_1	7^1	52	1	1
	1901-25	621	18^1_4	15_1	251	7	9

Table 7 16 Mortality[1] from Suicides by Sex Age Zygosity and Smoking Discordance Groups; Old Swedish Twin Registry B-series

	Born	DIZYGOTES No of Pairs	DIZYGOTES Pooled Low Group	DIZYGOTES Pooled High Group	MONOZYGOTES No of Pairs	MONOZYGOTES Pooled Low Group	MONOZYGOTES Pooled High Group
PRESENT AND FORMER SMOKERS							
Males	1911-25	501	1	6	177	0	3
	1901-10	205	1	0	69	1	0
	1901-25	706	2	6	246	1	3
Females	1911-25	588	2	5	262	0	3
	1901-10	193	0	0	64	0	0
	1901-25	781	2	5	326	0	3
PRESENT SMOKERS ONLY							
Males	1911-25	356	1	5	123	0	3
	1901-10	130	1	0	44	1	0
	1901-25	486	2	5	167	1	3
Females	1911-25	477	2	5	199	0	2
	1901-10	144	0	0	52	0	0
	1901-25	621	2	5	251	0	2

1) See footnote to table 7 11

Table 7 19 Mortality Ratios in Total and by Smoking in "Factor-positive versus "Factor-negative Individuals and Proportion of "Factor-positive cases in Total Group[1]; Old Swedish Twin Registry A-series (Condensed from Floderus 1974)

Factor	Mortality Ratios Total	Non-smokers	Smokers	Proportion of "Factor-positive cases
Financially I have not achieved what I hoped for	1 4	1 8	1 3	0 23
My position has involved too much responsibility	1 3	1 6	1 2	0 38
I have had lot of diffi culty in my marriage	1 4	3 5	0 9	0 09
I have ften been restles	1 4	1 8	1 3	0 18
I have often had difficul ties in falling asleep	1 6	2 0	1 4	0 12
I have ften felt somewhat uneasy in my work	1 7	2 3	1 5	0 07

Table 7 20 Age-Standardised Ratios f Observed Ove Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-twin Gross Mortality Coronary Heart Disease Mortality and Cancer Mortality by Sex and Zygosity; Old Swedish Twin Registry MZT-series

		DIZYGOTES Non Smoker	All Present Smokers	MONOZYGOTES Non-Smokers	All Present Smoker	TOTAL Non-Smokers	All Present Smokers
Gross Mortality	Male	0 90	1 11	0 98	1 00	0 92	1 09
	Females	0 92	1 34	0 94	1.30	0 93	1 33
	Total	0 91	1 27	0 95	1 21	0 92	1 27
Coronary Heart Disease	Males	0 76	1 56	0 81	1 51	0 78	1 55
	Females	1 04	1 39	1 00	0 31	1 03	1 10
	Total	0 94	1 45	0 94	0 70	0 94	1 26
Cancer	Males	0 76	0 99	0 63	0 95	0 69	1 01
	Females	0 94	1 89	1 05	0 93	0 98	1 60
	Total	0 90	1 67	0 97	0 94	0 92	1 48

1) The total group ize is dependant f varying non-response r tes for the different items but is mostly ca 5 000 individuals (for details see Floderus 1974)

7 3 4 Mortality and some risk factors other than smoking

Age adjusted mortality rates in the A-series fashion by smoking and two different expressions of alcohol behavior namely registration and excessive alcohol consumption (section 4 3 2) appear in table 7 18

Registration appears to be consistently associated with increased mortality in all age and smoking groups except for cigar/pipe smokers in the younger cohort and except for the highest cigarette consumption group in the older cohort The relationship is also found among nonsmokers It is also apparent that registration is related to smoking About one tenth of the nonsmokers are registered as against one fourth in the high cigarette consumption group

No such obvious trend was seen in regard to excessive alcohol consumption Only among those who smoked 10 or more cigarettes a day in the youngest cohort was a significant difference observed No effect of alcohol consumption was seen among nonsmokers

Table 7 19 presents mortality ratios in the A-series fashion calculated as the mortality rate among individuals who are positive with regard to a certain psycho-social factor (section 4 4) over the rate among individuals who are negative with regard to the same factor Rates have been

Table 7 18 Age-adjusted Mortality Rates by Age and Smoking Groups among Registered versus "Not Registered as well as among Excessive Alcohol Consumers versus Remaining Group ; Old Swedish Twin Registry Present and Former Smokers Males only A series

	Non-smokers		≤10 cigarettes		>10 cigarettes		Cigar/pipe	
Alcohol status	POS	NEG	POS	NEG	POS	NEG	POS	NEG
Registration								
No at Risk								
1911-25	144	1563	291	1342	264	768	188	859
1901-10	91	790	128	621	69	261	88	568
Rates								
1911-25	6 7	4 4	12 2	5 9	15 0	6 9	5 3	5 9
1901-10	25 1	15 3	27 8	18 0	33 3	33 3	27 1	18 8
Excessive consumption								
No at risk								
1911-25	359	1048	707	692	506	348	428	440
1901-10	146	540	235	370	110	137	178	322
Rates								
1911-25	3 4	3 3	5 0	4 1	8 0	4 6	5 1	3 6
1901-10	9 6	10 5	13 1	14 9	20 6	29 2	16 5	13 7

Table 7.19 Mortality Ratios in Total and by Smoking in "Factor-positive versus "Factor-negative Individuals and Proportion of "Factor-positive cases in Total Group[1]; Old Swedish Twin Registry A-series (Condensed from Floderus 1974)

Factor	Mortality Ratios: Total	Mortality Ratios: Non-smokers	Mortality Ratios: Smokers	Proportion of "Factor-positive cases
Financially I have not achieved what I hoped for	1 4	1 8	1 3	0 23
My position has involved too much responsibility	1.3	1 6	1 2	0 38
I have had a lot f diffi culty in my marriage	1 4	3 5	0 9	0 09
I have often been restless	1 4	1 8	1 3	0 18
I have often had difficul- ties in falling asleep	1 6	2 0	1 4	0 12
I have often felt somewhat uneasy in my work	1 7	2 3	1 5	0 07

Table 7 20 Age-Standardized Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status of Co-twin Gross Mortality Coronary Heart Disease Mortality and Cancer Mortality by Sex and Zygosity; Old Swedish Twin Registry NET-series

		DIZYGOTES		MONOZYGOTES		TOTAL	
		Non-Smokers	All Present Smokers	Non-Smokers	All Present Smokers	Non-Smokers	All Present Smokers
Gross Mortality	Males	0 90	1 11	0 98	1 00	0 92	1 09
	Females	0 92	1 34	0 94	1 30	0 93	1 33
	Total	0 91	1 27	0 95	1 21	0 92	1 27
Coronary Heart Disease	Males	0 76	1 56	0 81	1 51	0 78	1 55
	Females	1 04	1 39	1 00	0 31	1 03	1 10
	Total	0 94	1 45	0 94	0 70	0 94	1 26
Cancer	Males	0 76	0 99	0 63	0 95	0 69	1 01
	Females	0 94	1 88	1 05	0 93	0 98	1 60
	Total	0 90	1 67	0 97	0 94	0 92	1 48

1) The total group size is dependant of varying non-response rates for the different items but is mostly ca 5 000 individuals (for details see Floderus 1974)

7 3 4 Mortality and some risk factors other than smoking

Age adjusted mortality rates in the A-series fashion by smoking and two different expressions of alcohol behavior namely registration and excessive alcohol consumption (section 4 3 2) appear in table 7 18

Registration appears to be consistently associated with increased mortality in all age and smoking groups except for cigar/pipe smokers in the *younger cohort and except for the highest cigarette consumption group* in the older cohort The relationship is also found among nonsmokers It is also apparent that registration is related to smoking About one tenth of the nonsmokers are registered as against one fourth in the high cigarette consumption group

No such obvious trend was seen in regard to excessive alcohol consumption Only among those who smoked 10 or more cigarettes a day in the youngest cohort was a significant difference observed No effect of alcohol consumption was seen among nonsmokers

Table 7 19 presents mortality ratios in the A-series fashion calculated as the mortality rate among individuals who are positive with regard to a certain psycho-social factor (section 4 4) over the rate among individuals who are negative with regard to the same factor Rates have been

Table 7 18 Age-adjusted Mortality Rates by Age and Smoking Groups among Registered versus Not Registered as well as among Excessive Alcohol Consumers versus Remaining Group ; Old Swedish Twin Registry Present and Former Smokers Males only A-series

	Non-smokers		≤10 cigarettes		>10 cigarettes		Cigar/pipe	
Alcohol status	POS	NEG	POS	NEG	POS	NEG	POS	NEG
Registration								
No at Risk								
1911-25	144	1563	291	1342	264	768	188	859
1901-10	91	790	128	621	69	261	88	568
Rates								
1911-25	6 7	4 4	12 2	5 9	15 0	6 9	5 3	5 9
1901-10	25 1	15 3	27 8	18 0	33 3	33 3	27 1	18 8
Excessive consumption								
No at risk								
1911-25	359	1048	707	692	506	348	428	440
1901-10	146	540	235	370	110	137	178	322
Rates								
1911-25	3 4	3 3	5 0	4 1	8 0	4 6	5 1	3 6
1901-10	9 6	10 5	13 1	14 9	20 6	29 2	16 5	13 7

Table 7 19 Mortality Ratios in Total and by Smoking in "Factor-positive versus "Factor negative Individuals and Proportion of "Factor-positive cases in Total Group[1]; Old Swedish Twin Registry A-series (Condensed from Floderus 1974)

Factor	Mortality Ratios Total	Non-smokers	Smokers	Proportion of "Factor-positive cases
Financially I have not achieved what I hoped for	1 4	1 8	1 3	0 23
My position has involved too much responsibility	1 3	1 6	1 2	0 38
I have had a lot of diffi culty in my marriage	1 4	3 5	0 9	0 09
I have often been estles	1 4	1 8	1 3	0 18
I have often had difficul ties in falling asleep	1 6	2 0	1 4	0 12
I have often f lt somewhat uneasy in my work	1 7	2 3	1 5	0 07

Table 7 20 Age-Standardised Ratios of Observed Over Expected Prevalence Rates Among Nonsmokers Grouped by Smoking Status f Co-twin Gross Mortality Coronary Heart Disease Mortality and Cancer Mortality by Sex and Zygosity; Old Swedish Twin Registry NET-series

		DIZYGOTES		MONOZYGOTES		TOTAL	
		Non-Smokers	All Present Smokers	Non-Smokers	All Present Smokers	Non-Smokers	All Present Smokers
Gross Mortality	Males	0 90	1 11	0 98	1 00	0 92	1 09
	Females	0 92	1 34	0 94	1 30	0 93	1 33
	Total	0 91	1 27	0 95	1 21	0 92	1 27
Coronary Heart Disease	Males	0 76	1 56	0 81	1 51	0 78	1 55
	Females	1 04	1 39	1 00	0 31	1 03	1 10
	Total	0 94	1 48	0 94	0 70	0 94	1 26
Cancer	Males	0 76	0 99	0 63	0 95	0 69	1 01
	Females	0 94	1 98	1 05	0 93	0 98	1 60
	Total	0 90	1 67	0 97	0 94	0 92	1 48

1) The total group ize is dependant of varying non-response rates for the different items but is mostly ca 5 000 individuals (for details see Floderus 1974)

7 3 4 Mortality and some risk factors other than smoking

Age adjusted mortality rates in the A-series fashion by smoking and two different expressions of alcohol behavior *namely* registration and excessive alcohol consumption (section 4 3 2) appear in table 7 18

Registration appears to be consistently associated with increased mortality in all age and smoking groups except for cigar/pipe smokers in the younger cohort and except for the highest cigarette consumption group in the older cohort The relationship is also found among nonsmokers It is also apparent that registration is related to smoking About one tenth of the nonsmokers are registered as against one fourth in the high cigarette consumption group

No such obvious trend was seen in regard to excessive alcohol consumption Only among those who smoked 10 or more cigarettes a day in the youngest cohort was a significant difference observed No effect of alcohol consumption was seen among nonsmokers

Table 7 19 presents mortality ratios in the A-series fashion calculated as the mortality rate among individuals who are positive with regard to a certain psycho-social factor (section 4 4) over the rate among individuals who are negative with regard to the same factor Rates have been

Table 7 18 Age-adjusted Mortality Rates by Age and Smoking Groups among Registered versus Not Registered as well as among "Excessive Alcohol Consumers versus "Remaining Group ; Old Swedish Twin Registry Present and Former Smokers Males only A series

	Non-smokers		<10 cigarettes		>10 cigarettes		Cigar/pipe	
Alcohol status	POS	NEG	POS	NEG	POS	NEG	POS	NEG
Registration								
No at Risk								
1911-25	144	1563	291	1342	264	768	188	859
1901-10	91	790	128	621	69	261	88	568
Rates								
1911-25	6 7	4 4	12 2	5 9	15 0	6 9	5 3	5 9
1901-10	25 1	15 3	27 8*	18 0	33 3	33 3	27 1	18 8
Excessive consumption								
No at risk								
1911-25	359	1048	707	692	506	348	428	440
1901-10	146	540	235	370	110	137	178	322
Rates								
1911-25	3 4	3 3	5 0	4 1	8 0	4 6	5 1	3 6
1901-10	9 6	10 5	13 1	14 9	20 6	29 2	16 5	13 7

8 SUMMARY DISCUSSION AND CONCLUSIONS

8 1 Introduction

The presentation of the twin esearch program in thi report has so far involved an extensive description of methodological spects of the twin method as well as a detailed account of various results from a series of questionnaire studies clinical examinations and mortality follow-ups

Upon the initiation f the program in 1959 the intention was primarily to perform f llow-up in longitudinal manne of cohort of twins and to study mortality against the background of smoking habits When the lder cohort of twins born 1886-1925 was approached for the first time information was thus sought mainly about smoking habits and some similarity variables for determining zygosity At various tage during the course of time a seri of questionnaires were mailed to the twins asking for inf rmation about habitual factors other than smoking as well as about broader spectrum of disease experience In addition some detailed linical examinations were performed on subsamples of twins furnishing information to lucidate certain topic areas such as the relationship between tobacco smoking and coronary heart disease geneti aspects of spiratory and cardiovascular disease the influence of drinking on the endpoints studied and the importance f psycho-social factors for the smoking-disease association

The extension f the twin program in 1971 to include cohorts born 1926-1958 was motivated by the need to have base-line information on socio-economic behavior l psychological sociological and medical factors available for longitudinal investigations in the fi ld of environmental health Even though this extended program does not primarily focus on smoking and health in the long run it nonetheles furnishes mortality data that will supplement the analyses performed on the older cohorts of the egistry It has already been used to give information on the question of differences between various smoking and nonsmoking groups in regard to an extended series of variables

Upon the initiation f the twin program two major assumptions were made The first was that smokers differ from nonsmokers in many aspects relevant for developing disease and for increasing the risk f premature death The second sumption was that many such variabl would be more similar between the two members f twin-pair as compared to unrelated individuals even if the twins in pair wer dissimilar in regard to smoking

The present chapte will first assess to what extent the above mentioned assumptions have been supported by the data A second part of the chapter will evaluate whethe the results from the analysi on twin pairs have given information on the smoking-health relationship that devi tes from results obtained in conventional epidemiological analysis If so the question then is to what extent tudi on twin pairs yield information of recognizable epidemiological value and contribute to bette under tanding f the relationship between smoking and health

calculated both in total and separately for smokers and nonsmokers The last column presents the relative number of factor positives in the total group The table shows the 6 items out of a total of 15 where any of the mortality ratios proved to be statistically significant It is apparent from the table that psycho-social factors are related to mortality in smokers as well as nonsmokers The factors lastly are not too uncommon in the population The above presented analyses were both of the A-series type Corresponding B-series analysis can hardly be performed at present since the requirement of controlling for both smoking and the factor" would reduce the numbers drastically

7 3 5 *Mortality among nonsmoking partners of smoking co-twins*

Table 7 20 page 103 shows the results of a NET-analysis in regard to gross mortality mortality in coronary heart disease and cancer all sites It has due to low numbers not been possible to carry out a NET analysis on other specific causes of death

In the table data are given for the nonsmoking partners of nonsmoking co-twins as well as for the nonsmoking partners of presently smoking co-twins The groups are broken down by sex and zygosity and are also presented in subtotals and totals As usual standardization is performed over sex and age groups It is obvious from several subgroups that the mortality among the nonsmokers is significantly related to the smoking status of the partner Significant ratios are not seen among the monozygotes It should however be pointed out that some ratios are increased also in the monozygotes

common among the high smok rs and extravertness appeared to be moderately but significantly more common in the smoking groups as compared to nonsmokers

This consistent pictur was shown for men as well as for women There were no striking contrasts between age groups except that highe ratios were often found in the very youngest age groups compri ing boys and girls in the age range of 15-17 years For exampl in this age brack t drinking was up to 5 times more common among smokers than among nonsmokers (77 percent as against 13 percent); use of oral contraceptives was up to 9 times more common among the female smokers than among the femal nonsmokers (16 percent as against les than 2 percent)

8 2 3 Summary of results from studies on twin pairs

B-analyses of smoking discordant twin pairs the purpose of which is to measure the degree of control for the variables tudied were performed on nonsmokers against present cigarette smokers Observed ratios of the prevalence of risk factors among the smokers over the prevalence of such among the nonsmokers adjusted for sex age and smoking quantity were compared to expected ratios based on A-esti ates

The results showed learly that the observed ratios for most items were considerably lower than the expected tios and more often lower among monozygotes as compared to dizygotes For example in regard to drinking the monozygotic tio was 1 1 as compared to an expected ratio of 1 5 For excessive drinking the ratio was 1 5 as against 4 5 Examples of less good control are leeping pills and tranquillizers with observed ratios of 1 5 and 1 8 as against the expectations of 2 3 and 1 9

For traits where the ratio of the prevalence f smokers over that of nonsmokers in smoking discordant pairs was less than its expectation the prevalence among the nonsmoking partners was often higher than that among all nonsmokers This was studied for three groups of discordant pairs the partner being either a present cigarette smoker present smoker regardles of type or a forme smoker

It appeared for example that excessive drinking was 2 6 times more prevalent among monozygoti nonsmokers with partne presently smoking cigarettes as compared to all monozygoti nonsmokers in the twin series A further example from the same subgroup is provided by leeping pills with ratio f 1 2 Generally the monozygoti ratios tended to be higher than the dizygoti ones Only in exceptional cases were the ratios for nonsmoking partners of forme smokers ignificantly increased

For both monozygotes and dizygote the coincidence ratios with very few exceptions were higher than expected and almost consistently higher in the monozygoti series

The linical examinations compared smokers and nonsmokers with regard to for exampl blood pressure serum lipids and uric acid which are known biological risk factors in coronary heart disease Both blood pressure and cholesterol level were if anything negatively correlated to smoking in monozygotic pairs while phospholipids were moderately increased among smokers Not one single biological finding showed such pronounced difference between the smokers and nonsmokers as did the socioeconomic habitual and psycho-social items presented above

8 2 Group Comparability between Various Smoking and Nonsmoking Groups

8 2 1 Introductory remarks

In the introduction of chapter 6 a short review was given of the literature in regard to differences between smokers and nonsmokers Substantial evidence showing that smokers differ from nonsmokers in respect to many variables was found to exist

In the present report the group comparability has been further studied on a large number of variables and with due consideration paid to possible relations to amount and type of smoking as well as to associations with sex and age Thus the present study evaluates whether differences found between unrelated smokers and nonsmokers (A series) still existed or were fully or partly controlled between the partners in smoking dis cordant monozygotic and dizygotic twin pairs (B-series) A possible reflection of such control could also be that the nonsmoker in a smoking discordant pair due to genetic or environmental factors shows simila rities with his smoking partner while he at the same time differs from all nonsmokers of which the majority belongs to concordantly nonsmoking pairs (NET-analysis)

8 2 2 Summary of results from studies on unrelated individuals

The question of differences between smokers and nonsmokers has been elucidated on the basis of data mainly from the new twin registry The investigation covered several subject areas such as socioeconomic data and variables connected with education and occupation data on consumption of alcohol and some drugs certain food habits and variables indicating psycho-social discord

The socioeconomic picture of the smokers shows them more often to be living in apartments than in private homes less often to have an education beyond elementary school more often to change employment and to have overtime shiftwork and piecework

The most dramatic association was shown in regard to drinking and especially excessive drinking Consumers of more than 16 cigarettes a day drank excessive amounts of alcohol 3-10 times more often than the nonsmokers Sleeping pills and tranquillizers were used 3 5 times as often among the high cigarette smokers as among the nonsmokers The use of oral contraceptives among women was strongly related to amount of smoking

In regard to food smokers displayed higher prevalence of such somewhat unhealthy" habits as having only one warm meal or less a day and drink ing five or more cups of coffee a day Furthermore they displayed lower use of "healthy" food items such as fruits and vegetabl s

Indications of psycho-social discord were also related to smoking Sleeping difficulties and stress were thus reported about twice as often by the smokers in the highest cigarette smoking category as compared to nonsmokers Divorce was about four times as common among high smokers as among nonsmokers A personality measurement according to a special psycho-social scale showed that instability was up to three times so

8 3 Smoking Related Morbidity and Mortality

8 3 1 Introductory remarks

The results discussed in foregoing sections have clearly indicated that both assumptions presented in section 8 1 were strongly supported

Thus the first assumption was borne out because smokers and nonsmokers did differ in regard to almost all variables measured in the 1973 questionnaire tudy and the question is to what extent such variables may have an influence on the health status of the individual Some of them have previously been found to be related to disease and premature death socioeconomic and occupational variables (Larsson 1965; US Dept of HEW 1963) habitual factor (Klatsky Friedman and Siegelaub 1973 1974) and psycho-social status (Friedman and Rosenman 1959; Jenkins 1971; Ostfeld et al 1964; Jenkins Rosenman and Zyzanski 1968)

The second assumption that the modified twin control method as defined in the present report should offer a better group comparability than the conventional comparison of tudy groups - was also verified even if the control was not complete

The genotype identity among monozygotes by definition leads to an ideal group comparability in regard to constitutional factors As fo the habitual and psycho-social items studied almost all showed coincidence values that were ignificantly above expectation and almost consistently higher among monozygotes as compared to dizygotes The degree of control as discussed in section 8 2 3 was often pronounced particularly in monozygotic pair

The following sections will summarize results from the morbidity and mortality studies performed on the cohort born 1901 1925 The cohort born 1886-1900 was not included in the analysis due to their high age t the induction f the study and due to the fact that the numbers were low and would with few exceptions not have contributed much to the analysis

Section 8 3 2 will present results in regard to morbidity and mortality which are similar to what would have been obtained in a study on unselected nonsmoking and smoking individuals Section 8 3 3 will deal with the analyses on smoking discordant twin pairs in regard to gross mortality and more specifically in regard to mortality from lung cancer and coronary heart disease The conclusions will be presented in section 8 3 4

8 3 2 Summary of results from studies on unrelated individuals

The <u>morbidity</u> investigations show 1 arcut relationship between smoking and the symptoms cough and angina pectoris in both the Swedish registries and in the American registry Furthermore in the new Swedish registry stomach disorder back disorders impaired hearing migraine sthma long-lasting illness and ick leave mo than or equal to 3 months in row are 11 smoking related It is worth emphasizing that hypermorbidity ratios around 2 and 3 are not infrequently found among the last mentioned diseases and that some high ratios are also found in the very youngest age group and among individuals who smoke 7 cigarette day or less Such an example is back disorders which appear with a

8 2 4 Discussion and conclusions

The results of the comparison of smokers and nonsmokers as unrelated individuals show beyond doubt that smokers are different from nonsmokers within rather broad conceptual areas Men and women bear out this finding to about the same extent; very young smokers do not deviate from this picture but rather strengthen it There is no reasonable way of attributing these findings to methodological fallacies nor is there any reason to question their generalizability to the population at large The explanation of the findings can theoretically be environmental or genetic or both The smokers may simply have been living in a different environment from the nonsmokers but genetic differences may also have played a large role

There is no unobjectionable way of discriminating between the environmental and genetic influences in the twin model as applied here Certainly the coincidence in regard to several of the above mentioned traits especially the behavioral and psycho-social ones was significantly higher among the monozygotic pairs as compared to the dizygotic According to the classical twin method such a finding would indicate an influence of genetic factors However genetic heredity may be less influential than a construct variable that could be termed social heredity On the other hand it may be argued that social heredity may itself reflect genetic determination to some extent As the coincidence of the mentioned traits were also above expectation among the dizygotic twins this finding can hardly be explained solely by the genetic resemblance between siblings The concept of social heredity may thus reasonably be considered as supported The excess coincidence among the monozygotic pairs as compared to the dizygotic may also be environmentally influenced A certain pressure may have been exerted not only from within the pairs but also from an environment that expected the twins to behave alike

In regard to several traits the prevalence rate among nonsmokers in the discordant group proved to be significantly increased in comparison to all nonsmokers in the twin series These findings - whether genetically or environmentally d termined - motivate an assumption of a life-style parameter that expresses itself in the development of not only smoking behavior but also of a great variety of habitual traits Smoking could then be regarded as one of many indice of this parameter

and 26 22 respectively Analyses of ignificance show that the exces mortality is ignificant only for dizygotes and not for monozygotes but also that a direct statistical comparison between th distributions for the monozygotic and the dizygoti group does not reveal ignificant results In the group of smokers versus nonsmokers the dizygotes show a hypermortality of 55 37 fo males and 52 43 fo females Corresponding numbers among monozygoti pair we e 15 10 and 22 16 respectively The differenc is ignificant in mal dizygotes only As for the observed hypermortality among exposed monozygotes it is worth pointing out that the excess was found mainly in the younger age-group

The increased mortality in the monozygoti group was hardly seen during the first ten years of observation In the last five-year period however the hypermortality calculated as incidence ratios was no longer different between the zygosity groups This is true irrespective of whether former smokers were included or not in the analysis

The hypermortality in the dizygoti group expressed as a r tio is about 1 5 which i close to what can be expected on the basis both of the A-series and f the Swedish smoking study on 55 000 males and females (Cederlöf et al 1975) allowing mean discordance of about 7 8 cigarettes day

Among the cause-specifi deaths in the B-series analysis lung cancer reflects the findings in the A-series Among dizygoti males 9 cases occurred in the pooled high group against 2 cases in the pooled low group or if only smoker versus nonsmokers are considered 6 cases versus 1 case Among monozygoti males 3 cases occurred 2 in the pooled high group and 1 in the pooled low group The case in the low group was lso a smoker however In view of the importance of lung cancer as smoking related cause of death the low number of cases among the monozygotes prompted the analysis f data from the oldest cohort of twins born 1886-1900 (Cederlöf and Friberg to be published) It was found that 3 lung cancer deaths had occurred among 89 pairs in the dizygotic group and 3 deaths among 50 pairs in the monozygotic group All cases occurred in the high exposure group Taking 11 age groups together there were 12 cases in the pooled high group against 2 cases in the pooled low group among dizygotes Corresponding numbers fo the monozygotes were 5 against 1 Among females only 2 cases appeared 1 in the dizygoti pooled high group and 1 in the monozygotic pooled low group the last mentioned case also being a smoker

Other diagnoses of respiratory disorders as cause of death have not given great enough numbers to warrant any statistical treatment It should be mentioned in this connection that the morbidity studies in Sweden as well as in the US showed clearcut relationships not only in the A series analysis but lso in the B-series in regard to cough and prolonged cough Moreover the clinical investigation by Lundman (1966) showed that lung function tests were ignificantly impaired among smokers in both monozygoti and dizygoti pair

The mortality data on coronary heart disease analyzed in the B-series fashion on the pooled high and pooled low groups reveal distribution f deaths that is 25 13 for male and 11 for female dizygotic twins Among monozygoti twins the distribution is 10 8 for males Among femal monozygotes only 4 cases were observed of which 3 belonged to the pooled high smoking group and 1 to the lower group If only present smoker ar considered the numbers in the pooled high and pooled low mal groups were 18 7 among dizygotes and 6 6 among monozygotes

ratio of 2 9 among young males and 2 5 among young females Stomach disorders in the youngest and lowest smoking female groups show a hyper mortality ratio of 1 6 Sick leave for 3 months in a row or more appears with hypermorbidity ratios of 3 3 *and 2 5 among* the youngest males and females respectively in the lowest cigarette smoking group

The gross mortality is strongly related to present smoking the group smoking more than 10 cigarettes a day displaying hypermortality ratios of about 2 This is true for both men and women and in both age-groups Male former smokers who used to smoke more than 10 cigarettes daily also show similarly increased ratios

Gross mortality was also related to other risk factors Thus alcohol registration per se was associated with mortality in nonsmokers as well as smokers The mortality in several subgroups was about twice as high among registered as compared to non-registered These data fit well with results from the Swedish smoking study on 55 000 males and females (Cederlöf et al 1975)

Also certain psycho-social factors such as financial problems too much responsibility restlessness and sleeping difficulties were clearly related to mortality

Cause specific mortality ratios are found to be significantly increased for coronary heart disease lung cancer suicides and accidents in several subgroups

Death from coronary heart disease already shows an increase with relative risks of about 2 among those who smoke or smoked 10 cigarettes or less a day The ratio approaches 3 among the males who were smoking more than 10 cigarettes daily in 1961 Former smokers born 1901-1910 show similarly increased ratios

Lung cancer is closely related to amount smoked showing ratios of 5-6 in the lower and of 13-25 in the higher smoking category among males Former smokers show considerably lower hypermortality ratios but the low numbers make a quantification difficult

Increased ratios were also found for suicides and accidents 2-8 and about 2 respectively

8 3 3 Summary of results from studies on twin pairs

The analyses are generally based on separate statistical treatment of two *sets of discordance groups* of which the first set is confined to smokers versus nonsmokers; the second set of discordance groups also includes pairs where both are smokers but smoke different amounts (pooled high group versus pooled low group cf section 4 3 2) *This step has* been taken in order to gain in numbers Data were also treated with and without former smokers included Since the discrepancies between these groups in most cases were minor and in consideration of the fact that also former smokers in the A series showed elevated mortality ratios the following comments relate mostly to the group with former smok rs included

Among disygotic pairs there was an obvious hypermortality in th pooled high group compared with the pooled low group 82 54 for males and 60 44 for females Corresponding numbers among monozygotic pairs were 27 24

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Coronary heart disease as a morbidity entity was investigated in two separate clinical examinations In the Lundman study (1966) on smoking discordant twin pairs no higher prevalence rates were revealed among the smokers than among the nonsmokers In another clinical study (Liljefors 1970) on pairs discordant for coronary heart disease no significantly greater numbers of smokers were found among the diseased partners as compared to the nondiseased partners The Liljefors study instead suggested that variables of psycho-social character such as ambition and dedication to work have a greater impact on the development of the disease

MET-analyses were performed on morbidity data in the new twin registry in the same fashion as was done for non-medical data It was shown that the symptoms cough shortness of breath stomach disorders back disorders and migraine as well as sick leave for 3 months or more in a row occurred more often among monozygotic nonsmokers with a presently smoking partner than among all the nonsmokers in the twin series This was especially marked for males The ratios were significantly increased with values ranging from 1 3-1 9 Only in regard to stomach disorders were the ratios reliably increased for dizygotes Significantly increased ratios for back disorders and longlasting illness were found also among nonsmoking partners of former smokers

A MET analysis was also carried out on gross mortality mortality in coronary heart disease and cancer all sites The data have been treated in various subgroupings Differences were often found to the effect that nonsmokers in smoking discordant pairs had higher mortality rates than had the total group of nonsmokers

8 3 4 Discussion and conclusions

The analyses of data from the old twin registry when the twins are regarded as a series of unrelated individuals show results that by and large confirm the well established picture of smoking as an indisputable risk factor for disease and premature death To the extent gross and cause specific mortality data have been studied they correspond largely with results found in the Swedish study on 55 000 Swedish men and women and except for the increased suicidal ratios do not deviate to any greater extent from the results of the well known US and UK epidemiological studies on smokers and nonsmokers The prevalence rates are almost consistently dose-related Men and women differ in some respects such as cause-specific deaths from coronary heart disease and cancers other than that of the lung but broadly speaking there is nothing to indicate that women would be considerably less at risk than men within the same smoking categories

In the new twin registry only morbidity has been possible to study The associations between smoking and respiratory and c rdiovascular symptoms were confirmed Associations were however also found with a l rge number of indications of other symptoms of disease or ill health such as stomach disorders back disorders impaired hearing nd longlasting illness Such associations were found also in the very youngest age groups 15 17 years where taking exposure time and the low amounts of smoking into account the exposure must be considered low In regard to re pir tory symptoms it is not unreasonable that even a hort exposure could give rise to symptoms in susceptible individuals It i much more difficult to see how there could be a causal ssociation between smoking and for example back disorders longlasting illness and sick leave for three o

more months in a row in young people exposed to low amounts of tobacco for just few years On the contrary these findings support the evidence from the foregoing sections that the smokers should be overrepresented by peopl who are constitutionally different from nonsmokers or who quite generally indulge in unhealthy living Theoretically the results may also flect to some extent a tendency for smokers to over report physical ill feelings pos ibly due to differences in personality

The conventional picture revealed by the A-series analysi is by and large reflected in th B-seri analyses of dizygoti twins wher espiratory morbidity total mortality and death from sever l specific causes including lung cancer and coronary heart disease show increased relative isks among the mor exposed partners in the discordant pairs Generally these relative risks do not differ to any appreciable extent from what can be expected considering a mean discordance of about 7 cigarettes a day

The monozygoti picture agrees with the dizygotic in several respects but not in all The most triking imilarity between the two zygosity groups was found in egard to respiratory symptoms and lung cancer The well documented evidence of a causal associ tion between smoking and lung cancer found in other studie has been further supported

In regard to coronary heart disease the ituation is less clearcut Among males the dizygoti ratio of 1 9 i ignificant while the monozygotic rati of 1 2 i rather lose to zer If former smokers are excluded the corresponding r tios ar 2 6 and 1.0 respectively the latter r ti however being based on the distribution of 12 cases only The outcome nevertheless suggests a difference between the two zygosity series even if the monozygoti number are too small to warrant more firm conclusions

Concerning the gross mortality it has earlier been pointed out (Friberg et al 1973) that no hypermortality t that time was seen in the monozygoti pooled high group There i still no statistically significant hypermortality related to smoking in the monozygoti groups Looking t the picture as a whol however (table 7 11) there are ther consistent tendencies towards excess death lso in the monozygoti group This is due to an increased incidence during the last 5-year period

It is obvious that suicides considerably and to some extent also accidents contribute to the hypermortality in smoker Pooling male and females and monozygotes and dizygotes 17 suicides have taken place in the pooled high groups as gainst 5 in the pooled low groups which gives a r tio f 3 4 Although sui ides and accidents are associ ted with smoking it has not been considered reasonable to assume that they are causally related to smoking Certainly from theo tical point of view suicides can be assumed to be precipitated by the awareness of serious somati disease and that smoking may cause accidental fires There was nothing whatsoever in the medical records including information from autopsies that indicated such an explanation Instead it indicates that among smokers there is an overrepresentation of indi iduals with an increased risk for committing suicides The findings seem to be yet another indication of the incomparability of smokers and nonsmokers

Still another problem in comparing smokers and nonsmokers is reflected by the high rate f egistered" among the smokers In the twin studies and the Swedish probability sampl (Cederlöf t al 1975) it is shown beyond doubt that regi tr tion with all its implications of alcohol

abuse and asocial behavior is not only associated with smoking but is a considerable risk factor per se as demonstrated by increased rates also among registered nonsmokers Because of low numbers it has not as yet been possible to make a detailed analysis in the B-series fashion

There are some unpublished mortality data *from the US twin registry* which are of interest also in this context (Hrubec Cederlöf and Friberg to be published) In the analysis of 1403 dizygotic and 1113 monozygotic smoking discordant[1] twin pairs 61 deaths were observed in the dizygotic pooled high group as against 42 in the pooled low group Corresponding numbers in the monozygotic group were 45 against 31 Thus a hyper-mortality related to smoking was found in both zygosity groups When however pairs with discordant or unknown drinking habits were excluded from the total group it was found that 25 deaths had occurred in the high smoking group as against 25 deaths in the low smoking groups among 729 smoking discordant dizygotic twin pairs Corresponding numbers of deaths among 640 monozygotic pairs were 21 and 20 respectively If the group "high smokers and high drinkers are compared to their low smoking and low drinking co-twins the numbers of deaths were 21 as against 10 *for dizygotes and 11 as against 5 for monozygotes The reason for* the different results in the different subgroups is not clear It is however not possible to explain it by differences in smoking habits At least two possible explanations exist namely that there is either an interactive effect of alcohol and tobacco or selective effects implying that the presence of both habits in an individual indicates a certain constitutional selection

A question of importance for the total assessment of the differences found between the monozygotic and dizygotic groups is to what extent the smoking discordance is comparable This has been discussed extensively in section 4 6 2 and it can be concluded that even if minor differences may have existed they should not have been of decisive importance In addition the data on lung cancer further support such a statement

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1) The discordance classification differs somewhat from the one used in the present report

8 4 Smoking and Health in the Perspective of Twin Research

Studies on smoking and health have to a great extent focused on lung cancer and coronary heart disease Gross mortality obviously is also of great concern not only due to the fact that the two mentioned diseases particularly coronary heart disease constitute major causes of death but also due to the fact that a great vari ty of other diseases have been laimed to be causally associated with smoking In the present evaluation it has howeve not been pos ibl to divide gross mortality into more than few subgroups

As for lung cance so much data have accumulated during the last decades that there should be no doubt about causal link between smoking and the development of the disease However the constitutional hypothesis a advanced by Fisher and still supported by a few has here been tested in twin tudies The results from the Swedish monozygotic twin series speak strongly against this constitutional hypothesis Constitution may still be of importance however in the way that certain individuals may be more susceptible It has thus been pointed out that the enzyme aryl hydrocarbon hydroxylase (AHH) may be genetically determined and mediate an increased susceptibility to certain carcinogens found in tobacco smoke

Chroni bronchitis i generally considered to be closely associated with smoking This disease entity is not common cause of death in Sweden and no evaluation can be made based on th present mortality data The prevalence of different degrees f cough was however strongly associ ted with smoking in both dizygotic and monozygotic smoking discordant pair There could be no doubt that such respiratory symptoms are causally associated with smoking even if the data suggest that constitutional factors fo susceptible individual may be of the same importance as is smoking f the development of the disease

Mortality in coronary heart disease has in a number of epidemiological studies been associ ted with smoking A imilar association was found among unrelated individuals in the Swedish twin studies as well as in the ecent Swedish study on 5 000 men and women Even though the hyper mortali y tios are generally considerably lower than those for lung cance nonetheles the absolute number of excess deaths among smokers i considerably higher on the population scale due to the high incidence of coronary heart disease

The l of smoking in the pathogenesis of this disease is much more open as it is multifactorial disease where several risk factor play an important part and where these may be strongly interrelated One of the easons for initiating the present research program was the assumption that such isk factors to great extent could be correlated with smoking and that when studying smoking discordant pairs the risk factors would be more similar between th members of smoking discordant monozygoti pairs than in dizygoti pairs or between smokers and nonsmokers among unr l ted indi iduals The results from smoking discordant twins sugges that the hypermortality among monozygotic pairs may distribute differently as compared with the dizygotic pairs and the A-series These data re however not yet conclusive due to low numbers Great care should be exercised in interpreting this finding especially as the gross morta lity incidence ratio has increased in the monozygotic group during the

last five years of observation indicating possible biasing effects due to censoring Such bias is more likely to influence the outcome during the first years of observation As in the dizygotic group there was a hypermortality already during the first period The outcome may just as well indicate that other factors than smoking play an essential part in the etiology of coronary heart disease i e factors which are less discordant in the monozygotic than in the dizygotic pairs Such an assumption is also congruent with the results reported by Lundman (1966) and Liljefors (1970) in their clinical studies on smoking discordant and coronary heart disease discordant twins There is also all reason to believe that genetic factors may play an important role also in the development of coronary heart disease This was well documented by de Faire (1974) in his study on death discordant twins where he found that the surviving partner of deceased twins with a diagnosis of coronary heart disease more often had symptoms and signs of this disease

Suicides and to some extent accidents occur to a significantly higher extent among smokers Out of 7 suicides in the monozygotic discordance groups 6 are found among the high exposed twins If smoking is held to be unlikely as a causative factor for suicides the estimate of hypermortality is no doubt unduly influenced by the suicide rate

As the major part of the data from the Swedish twin registry is based on questionnaire information and subsequent mortality follow-ups it has not been possible to study to any great extent physiological risk factors Instead the emphasis has been put on behavioral and psycho-social variables as well as on genetic interactions

The results clearly show that differences have been revealed for a large number of behavioral and psycho-social items also in very young people smoking only a few cigarettes a day The smokers deviated from the nonsmokers not only with regard to behavioral and psycho-social data; they did so also with respect to some effect variables such as back disorders and continuous sick leave for long periods where the causal link to smoking seems remote Further support for differences between smokers and nonsmokers was provided by very high hypermortality ratios for suicides The associations between smoking and registration in an alcohol registry point in the same direction The finding that several habitual risk factors as well as morbidity and mortality in the HET analysis were increased among nonsmokers if they had partners that were classified as present smokers indicates that smoking may be influenced by both genetic and social heredity

The results fit a model in which nonsmokers and smokers are different in regard to a life-style parameter of which smoking is but one index others being alcohol drinking drug abuse psycho-social discord etc It may be assumed that this parameter ranges from a healthy value at the one extreme to an unhealthy" value at the other extreme The concordant nonsmokers probably have values close to the first mentioned extreme and concordant smokers close to the other leaving the discordant smokers to occupy more undecided values in the middle of the range If this construct variable is associated with disease which is highly probable it is obvious that nonsmok rs in discordant pairs should experience ill health to a higher degree than concordant nonsmokers Whether the basic explanation is predominantly genetic o environmental may be open for speculation However from the analysis of the twin pairs it does seem that monozygotes as a rule fit the model better than dizygotes as demonstrated by better control of most habitual

and psycho-social traits higher coincidence and more pronounced life-style effects in th XCT-analysis These data point towards at least some influence f geneti factors

Even if quantitative assessments presently cannot be made of the rel tive roles of smoking ther risk factors and genetic disposition it seems that epidemiological investigations that have not controlled for factors referred to above may have overestimated the role of smoking as causative factor in coronary heart disease and lso considering for example the distribution of suicides among smokers and nonsmokers that such studies have more than duly made smoking responsible as a causative factor for all excess deaths seen in smokers On the other hand this should not be taken as evidence that smoking should be irrelevant as precipitating factor for deaths in for exampl coronary heart disease It seems for exampl obvious that carbon monoxide level reached in blood lready in moder te smokers may be deleterious in subjects with impaired coronary circulation (WHO 1975)

The esults from the twin tudy clearly demonstrate the importance of genetic several behavioral and psycho-social factors which have not been considered in conventional epidemiological studies Such factors should as far as possibl be included in future epidemiological research not only in the context of smoking and health but also in tudies on other imilar exposure factors that may be linked to risk factors of thi type or to geneti predispositions The twin approach certainly enhances the group comparability to considerable extent not only in regard to geneti but also with respect to habitual and psycho-social factors that may be f tiologi relevance The major drawback of the twin method is the question f numbers difficulty however that can be esolved by integrating data from several research center using the twin method Such programs ar under way

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REFERENCE LIST

Alexanderson B Evans D A P Sjöqvist F Steady-state plasma levels of nortriptyline in twins Influence of genetic factors and drug therapy Brit Med J 4 764 768 1969

Allen G Harvald B Sheilds J Measures of twin concordance Acta Genet 17 475-481 1967

Anderson E W Andelman R J Strauch J M Fortuin N J Knelson J H Effect of low-level carbon monoxide exposure on onset and dur tion of angina pectoris Ann Intern Med 79 46-50 1973

Backman R Studi s on the serum gamma-A-globulin level III The frequency of A-gamma-A globulinemia Scand J Clin Lab Invest 17 316-320 1965

Berkson J Smoking and lung cancer Some observations on two recent reports JASA 53 28-38 1958

Biörck G Contrasting concepts f ischaemic heart disease Almqvist and Wiksell Stockholm 1975

Björkman N M A comparison between postal questionnaire and interview methods in collection of data on alcohol abuse SOU 77 4 3-15 1971 (in Swedish)

Blackburn H Keys A Simonson E Ra tahar j P Punsar S The el ctro-cardiogram in population tudies A classification system. Circulation 21 1160-1175 1960

Blomstrand R Lundman T Serum lipids smoking and heredity In Lundman T Smoking in relation to coronary heart disease and lung function in twins Acta Med Scand suppl 455 1966

Brown B B Additional characteri ti EEG differences between smokers and nonsmoker In Smoking behavior Motives and incentives Ed W L Dunn Winston and Sons Washington D C 1973

Bulmer M G Th familial in idence f twinning Ann Hum Genet 24 1 3 1960

Burch P R J Problems in the interpretation of cancer statistics with special reference to lung cancer J Soc Occup Med 25 2 10 1975

Camner P Philipson K Friberg L Tracheobronchial clearance in twins Arch Environ Health 24 82-87 1972

Cavalli-Sforza L L Bodmer W F The genetics of human populations W H Freeman and Company San Francisco 1971

Cederlöf R Th twin method in epidemiologic studies on chroni disease Diss Acad University of Stockholm 1966

Cederlöf R Edf rs M-L Friberg L Jonsson E Hereditary factors Spontaneou cough and Smokers cough A study on 7 800 twin-pairs with the aid of mailed questionnaire Arch Environ Health 14 401-406 1967

Dorn H F The mortality of smokers and nonsmokers Proc Soc Stat Sect Amer Stat As 34 71 1958

Dorn H F Tobacco consumption and mortality from cancer and other diseases Public Health Rep 74 581 593 1959

Edwards A L Techniques f ttitude scale construction Appl ton-Century Crofts New York 1957

Ellis R A Endo C M Armer J M The use of potential nonrespondents f studying nonresponse bias Pac Soc Rev 13 103-109 1970

Epstein F H The epidemiology of coronary heart disease A review J Chron Dis 18 735-774 1965

Epstein F H Hyperglycemia A risk factor in coronary heart disease Circulation 36 609-619 1967

Eriksson S Studies in alpha$_1$-antitrypsin deficiency Acta Med Scand suppl 432 1965

Essen-Möller E Empirische Ähnlichkeitsdiagnose bei Zwillingen Hereditas 27 1 50 1941

Eysenck H J Smoking health and personality Basic Books New York 1965

Eysenck H J Eysenck S B G Manual f the Eysenck personality inventory University of London Pre London 1964

de Faire U I chemi heart disease in death discordant twins Acta Med Scand suppl 568 1974

de Faire U Friberg L Lorich U Lundman T A validation of cause-of death certification in 1156 deaths Acta Med Scand 200 223 228 1976

de Faire U Friberg L Lundman T Concordance for mortality with special ref rence to ischemi heart disease and cerebrovascular disease Prev Med 4 509-517 1975

Fisher R A Lung cancer and cigarettes Nature 182 108 1958

Fisher R A Cancer and smoking Natur 182 596 1958

Fisher R A Smoking the cancer controversy Some ttempts to assess the evidence London 1959

Floderus B Psycho-social f ctors in lation to coronary heart disease and associ ted isk f ctors Nord Hyg T suppl 6 1974

Fredrickson D S Mutants hyperlipoproteinaemia and coronary artery disease Brit Med J 2 187 192 1971

Friberg L Cederlöf R Lorich U Lundman T de Faire U Mortality in twins in relation to smoking habits and alcohol problems Arch Environ He lth 27 294-304 1973

F iberg L Kaij L Dencker S J Jonsson E Smoking habits of monozygoti and dizygoti twins Brit Med J 1 1090-1092 1959

Cederlöf R Friberg L Lung cancer in twins To be published

Cederlöf R Friberg L Hrubec Z Cardiovascular and respiratory symptoms in relation to tobacco smoking A study on American twins Arch Environ Health 18:934 940 1969

Cederlöf R Friberg L Hrubec Z Lorich U The relationship of smoking and some social covariables to mortality and cancer morbidity A ten-year follow up in a probability sample of 55 000 Swedish subjects age 18 to 69 The Department of Environmental Hygiene The Karolinska Institute Stockholm 1975

Cederlöf R Friberg L Jonsson E The epidemiological approach in estimating MAC values with special reference to medico-sociological and statistical methodology Nord Hyg T 46 33-43 1965

Cederlöf R Friberg L Jonsson E Hereditary factors and angina pectoris Arch Environ Health 14:397 400 1967

Cederlöf R Friberg L Jonsson E Kaij L Studies on similarity diagnosis in twins with the aid of mailed questionnaires Acta Genet 11 338-362 1961

Cederlöf R Jonsson E Lundman T On the validity of mailed questionnaires in diagnosing angina pectoris and bronchitis Arch Environ Health 13 738 742 1966

Cerasi E Luft R Insulin response to glucose infusion in diabetic and non-diabetic monozygotic twin pairs Genetic control of insulin response? Acta Endocrinol 55 330-345 1967

Cochran W G Cox G M Experimental designs John Wiley and Sons New York 1960

Cole R B Nevin N C Blundell G Merret J D McDonald J R Johnston W P Relation of alpha 1-antitrypsin phenotype to the performance of pulmonary function tests and to the prevalence of respiratory illness in a working population Thorax 31 149-157 1976

College of General Practitioners British Medical Research Councills Committee on the aetiology of chronic bronchitis Standardized questionnaire on respiratory symptoms Brit Med J 2 1665 1960

Cooper D M Hoeppner V Cox D Zamel N Bryan A C Levison H Lung function in alpha$_1$ antitrypsin heterozygotes (PI type MZ) Amer Rev Resp Dis 110 708-715 1974

Deane G Keane T An investigation of the high twinning rate in the Republic of Ireland Brit J Prev Soc Med 26 186-192 1972

Doll R Hill A B Lung cancer and other causes of death in relation to smoking Second report on the mortality of British doctors Brit Med J 2 1071 1081 1956

Doll R Peto R Mortality in relation to smoking 20 years observations on male British doctors Brit Med J 2 1525-1536 1976

Dorn H F The mortality of smokers and nonsmokers Proc Soc Stat Sect Amer Stat As 34 71 1958

Dorn H F Tobacco consumption and mortality from cancer and other diseases Public Health Rep 74 581 593 1959

Edwards A L Techniques of ttitude scal construction Appleton-Century Crofts New York 19 7

Ellis R A Endo C M Armer J M The use of potenti l nonrespondents for tudying nonresponse bias Pac Soc Rev 13 103-109 1970

Epstein F H The epidemiology of coronary heart disease A eview J Chron Dis 18 73--774 1965

Epstein F H Hyperglycemia A risk factor in coronary heart disease Circulation 36 609-619 1967

Eriksson S Studies in lpha$_1$-antitrypsin deficiency Acta Med Scand suppl 432 1965

Essen-Möller E Empirische Ähnlichkeitsdiagnose bei Zwillingen Hereditas 27 1 50 1941

Eysenck H J Smoking health and personality Basic Books New York 1965

Eysenck H J Eysenck S B G Manual of the Eysenck personality inventory University of London Pre London 1964

de Faire U Ischemic heart disease in death discordant twins Acta Med Scand suppl 568 1974

de Faire U Friberg L Lorich U Lundman T A validation of cause-of death certification in 1156 deaths Acta Med Scand 200 223-228 1976

de Faire U Friberg L Lundman T Concordance for mortality with special reference to ischaemi heart disease and cerebrovascular disease Prev Med 4 509-517 1975

Fisher R A Lung cancer and cigarette Nature 182 108 1958

Fisher R A Cance and smoking Nature 182 596 1958

Fisher R A Smoking the cancer controversy Some ttempts to assess the evidence London 1959

Floderus B Psycho-social factors in relation to coronary heart disease and associ ted risk factors Nord Hyg T suppl 6 1974

Fredrickson D S Mutants hyperlipoproteinaemia and coronary artery disease B it Med J 2 187 192 1971

Friberg L Cederlöf R Lorich U Lundman T de Faire U Mortality in twins in relation to smoking habits and alcohol problems Arch Environ Health 27 294-304 1973

Friberg L Kaij L Dencker S J Jonsson E Smoking habits of monozygotic and dizygoti twins Brit Med J 1 1090-1092 1959

Cederlöf R Friberg L Lung cancer in twins To be published

Cederlöf R Friberg L Hrubec Z Cardiovascular and respiratory symptoms in relation to tobacco smoking A study on American twins Arch Environ Health 18 934 940 1969

Cederlöf R Friberg L Hrubec Z Lorich U The relationship of smoking and some social covariables to mortality and cancer morbidity A ten year follow-up in a probability sample of 55 000 Swedish subjects age 18 to 69 The Department of Environmental Hygiene The Karolinska Institute Stockholm 1975

Cederlöf R Friberg L Jonsson E The epidemiological approach in estimating MAC values with special reference to medico-sociological and statistical methodology Nord Hyg T 46:33-43 1965

Cederlöf R Friberg L Jonsson E Hereditary factors and angina pectoris Arch Environ Health 14 397-400 1967

Cederlöf R Friberg L Jonsson E Kaij L Studies on similarity diagnosis in twins with the aid of mailed questionnaires Acta Genet 11 338-362 1961

Cederlöf R Jonsson E Lundman T On the validity of mailed questionnaires in diagnosing angina pectoris and "bronchitis Arch Environ Health 13 738-742 1966

Cerasi E Luft R Insulin response to glucose infusion in diabetic and non-diabetic monozygotic twin pairs Genetic control of insulin response? Acta Endocrinol 55 330-345 1967

Cochran W G Cox G M Experimental designs John Wiley and Sons New York 1960

Cole R B Nevin N C Blundell G Merret J D McDonald J R Johnston W P Relation of alpha-1-antitrypsin phenotype to the performance of pulmonary function tests and to the prevalence of respiratory illness in a working population Thorax 31 149 157 1976

College of General Practitioners British Medical Research Councils Committee on the aetiology of chronic bronchitis Standardized questionnaire on respiratory symptoms Brit Med J 2 1665 1960

Cooper D M Hoeppner V Cox D Zamel N Bryan A C Levison H Lung function in alpha$_1$ antitrypsin heterozygotes (PI type MZ) Amer Rev Resp Dis 110 708-715 1974

Deane G Keane T An investigation of the high twinning rate in the Republic of Ireland Brit J Prev Soc Med 26 186-192 1972

Doll R Hill A B Lung cancer and other causes of death in relation to smoking Second report on the mortality of British doctors Brit Med J 2 1071-1081 1956

Doll R Peto R Mortality in relation to smoking 20 years observations on male British doctors Brit Med J 2 1525-1536 1976

Harvald B Hauge M Coronary occlusion in twins Acta Genet Med Gemellol 19:248-250 1970

Hauge M Harvald B Fisher M Gottlieb-Jensen K Juel-Nielsen N Raebild I Shapiro R Videbech T The Danish twin register Acta Genet Med Gemellol 17 315-331 1968

Hauge M Harvald B Reid D D A twin study of the influence of smoking on morbidity and mortality Acta Genet Med Gemellol 19 335-336 1970

Heath C W Differences between smokers and nonsmokers Arch Intern Med 101 377 388 1958

Higgins M W Keller J Familial occurrence of chroni respiratory disease and familial resemblance in ventilatory capacity J Chron Dis 28 239-251 197

Higgins M W Kj lsberg M Characteristi of smoker and nonsmokers in Tecumseh Michigan II The distribution of selected physical measurements and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers Amer J Epidemiol 86 60-77 1967

Higgins M W Kjelsberg M Metzner H Characteristics of smoker and nonsmokers in Tecumseh Michigan I The di tribution of smoking habits in persons and families and their elationship to social characteristics Amer J Epidemi l 86 45-59 1967

Horn D Changes in smoking patterns in the United States In Abstracts f the XIth International Cancer Congress Florence Symposium 36 20-26 Oct 1974

Hrubec Z The effect on diagnosti ascertainment in twins on the assessment of the geneti factor in disease ti logy Amer J Hum Genet 25 15-28 1973

Hrubec Z Allen G Methods and interpr tation f twin concordance data Amer J Hum Genet 27 808-809 1975

Hrubec Z Cederlöf R Friberg L Background of angina pectoris Social and environmental factors in rel tion to smoking Amer J Epidemiol 103 16-29 1976

Hrubec Z Cederlöf R Friberg L Mortality in US twins in relation to tobacco smoking and alcohol use To be published

Hrubec Z Cederlöf R Friberg L Horton R Ozolins G Respir tory symptoms in twins Effects of esidence associated ir pollution tobacco and lcohol use and ther factor Arch Environ Health 27 189-195 1973

Husén T Twin studies Lund 1953 (in Swedish)

Jablon S Neel J V Gershowitz H Atkinson G F The NAS-NRC twin panel Methods f construction f the panel zygosity diagnosis and proposed use Ame J Hum Genet 19 133-161 1967

Jenkins C D Psychologi and soci l precursor of coronary disease New Engl J Med 284 244 255 and 307 317 1971

Friedman G D A potential pitfall in studying trait-discordant twins To be published in Am J Epidemiol

Friedman G D Klatsky A L Siegelaub A B McCarthy M Kaiser-Permanente epidemiologic study of myocardial infarction Amer J Epidemiol 99:101 116 1974

Friedman G D Seltzer C C Siegelaub A B Feldman R Collen M F Smoking among white black and yellow men and women Kaiser-Permanente multiphasic health examination data 1964-1968 Amer J Epidemiol 96 23 35 1972

Friedman G D Siegelaub A B Seltzer C C Cigarette smoking and exposure to occupational hazards Amer J Epidemiol 98 175-183 1973

Friedman G D Siegelaub A B Seltzer C C Cigarettes alcohol coffee and peptic ulcer New Engl J Med 290:469-473 1974

Friedman G D Siegelaub A B Ury H K Klatsky A L Is the increased risk of myocardial infarction in cigarette smokers due to psychological traits? Prev Med 4:526-532 1975

Friedman M Rosenman R H Association of specific overt behavior pattern with blood and cardiovascular findings Blood cholesterol level blood clotting time incidence of arcus senilis J Amer Med Ass 169:1286-1296 1959

Gertler M M White P D Coronary heart disease in young adults - a multidisciplinary study Harvard University Press Cambridge Mass 1954

Gesell A The method of co-twin control Science 95:446-448 1942

Glass H B Genetic aspects of adaptability Res Publ Ass Res Nerv Ment Dis 33 367 377 1954

Goldstein J L Hazzard W R Schrott H G Bierman E L Motulsky A G Hyperlipidemia in coronary heart disease I Lipid levels in 500 sur vivors of myocardial infarction J Clin Invest 52 1533 1543 1973

Gsell O R Abelin T Cigar and pipe smoking in relation to lung cancer and excess mortality J Natl Cancer Inst 48 1795-1803 1972

Haas C Enfisema polmonare precoce e deficit di alfa-1-antitripsina Minerva Med 65 999-1003 1974

Haenszel W Shimkin M B Miller H P Tobacco smoking patterns in the United States Public Health Monogr 45 US Department of Health Educa tion and Welfare Washington D C 1956

Hammond E C Garfinkel L Seidman H Longevity of parents and grand parents in relation to coronary heart disease and associated variables Circulation 43 31 44 1971

Hammond E C Horn D Smoking and death rates report on forty-four months of follow-up of 187 783 men J Amer Med Ass 166:1159-1172 and 1294-1308 1958

Harvald B Hauge M Hereditary factors elucidated by twin studies Genetics and the epidemiology of chronic diseases Acta Med Scand suppl 445 1965

Laur 11 C B Erikason S The lectrophoretic lpha$_1$-globulin pattern of serum alpha$_1$-antitrypsin deficiency Scand J Clin Invest 15 132 140 1963

Leeder S R Role of infection in the cause and course of chronic bronchitis and emphysema J Infect Dis 131 731 742 197*

Leigh D Marley E Bronchial sthma. A genetic popul tion and psychiatri tudy Pergamon Pres Oxford 1967

Lieberman J Heterozygous and homozygous alpha$_1$-antitrypsin deficiency in patients with pulmonary emphysema New Engl J Med 281 279-284 1969

Lieberman J Alpha$_1$-antitrypsin deficiency Med Clin North Amer 57 691 706 1973

Lilienfeld A M Emotional and other selected char cteristics of cigarette smoker and nonsmokers related to epidemiological studie f lung ance and other diseases J Natl Cancer Inst 22 259-282 1959

Lilj for I Coronary heart disease in mal twins Hereditary and environmental factors in concordant and discordant pairs Acta Med Scand suppl 511 1970

Liljefors I Coronary heart disease in mal twins Seven-year follow-up of discordant pairs First International Congress of Twin Studies Rome 1974 To be published in Acta Genet Med Gemellol 1977

Longstr th G F Weitzman S A Browning R J Lieberman J Bronchiecta i and homozygous lpha$_1$-antitrypsin deficiency Chest 67 233-235 1975

Lundman T Smoking i lation to coronary heart disease and lung function in twins Acta Med Scand suppl 455 1966

Lundman T Lilj fors I Cederlöf R Friberg L The validity f the questionnaire diagnosi angina pectori Arch Environ Health 22 597 599 1971

McMahon B Pugh T F Ipsen J Epidemiologi methods Littl Brown and Co Boston 1960

Medlund P Cederlöf R Floderus-Myrhed B Friberg L Sörensen S A new Swedish twi registry Acta Med Scand suppl 600 1977

Meyer K Serum chol sterol and he edity A twin study Acta Med Scand 172 401-404 1962

Mittman C Lieberman J Rumsf ld J Prevalence of abnormal protease inhibitor phenotypes in patients with chroni obstructive lung disease Amer Rev Resp Di 109 295-296 1974

Morton N E Chung C S Mi M P Genetics f interraci l crosses in Hawaii S Karger New York 1967

Myrhed M Alcohol consumption in rel tion to factors associated with ischaemi heart disease Acta Med Scand suppl 567 1974

Jenkins C D Rosenman R H Zyzanski S J Cigarette smoking Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study Circulation 38:1140-1155 1968

Jensen J Blankenhorn D H Chin H P Sturgeon P Ware A G Serum lipids and serum uric acid in human twins J Lipid Res 6 193-205 1965

Johansson S G Högman C F Killander J Quantitative immunoglobulin determination Comparison of two methods Estimation of normal levels and levels in persons lacking IgA and IgD Acta Pathol Microbiol Scand 74:519-530 1968

Jonsson E Nilsson T Alcohol consumption in monozygotic and dizygotic twin pairs Nord Hyg T 49 21-25 1968 (in Swedish)

Kahn H A The Dorn study of smoking and mortality among US veterans Report on 8 1/2 years of observation Natl Cancer Inst Monogr 19:1-125 1966

Kaij L Alcoholism in twins Studies on the etiology and sequels of abuse of alcohol Almqvist and Wiksell Stockholm 1960

Kaplan S Cole P Factors affecting response to postal questionnaires Brit J Prev Soc Med 24 245-247 1970

Kastenbaum M A Lamphiear D E Calculation of Chi-square to test the no three-factor interaction hypothesis Biometrics 15:107-115 1959

Kellermann G Shaw C R Luyten Kellermann M Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma New Engl J Med 289 934 937 1973

Keys A Coronary heart disease - the global picture Atherosclerosis 22 149 192 1975

Keys A Aravanis C Blackburn H van Buchem F S P Buzina R Djordjevic B S Fidanza F Karvonen M J Menotti A Puddu V Taylor H L Coronary heart disease Overweight and obesity as risk factors Ann Intern Med 77 15-27 1972

Klatsky A L Friedman G D Siegelaub A B Coffee drinking prior to acute myocardial infarction Results from the Kaiser Permanente epidemiologic study of myocardial infarction J Amer Med Ass 226 540-543 1973

Klatsky A L Friedman G D Siegelaub A B Alcohol consumption before myocardial infarction Results from the Kaiser Permanente epidemiologic study of myocardial infarction Ann Intern Med 81 294-301 1974

Krueger D E Rogot E Blackwelder W C Reid D D The predictive value of a postal questionnaire on cardio-respiratory symptoms J Chron Dis 23 411-421 1970

Larsson T Mortality in Sweden Acta Genet Et Stat Med suppl 15 1965

Larson R K Barman M L Kueppers F Fudenberg H H Genetic and environ mental determinants of chronic obstructive pulmonary disease Ann Intern Med 72:627-632 1970

Sterling T D A critical reassessment of the evidence bearing on smoking as the cause of lung cancer Amer J Public Health 65 939-953 1975

Surgeon General Reports

The Surgeon General Advisory Committee Smoking and health US Department of Health Education and Welfare Washington D C 1964

National Clearinghouse for Smoking and Health The health consequences f smoking A Public Health Service Review US Department of Health Education and Welfar Washington D C 1967

1968 Supplement to the 1967 Public Health Service Review 1968

1969 Supplement to the 1967 Public Health Service Review 1969

The Surgeon General Health consequences of smoking A report of the Surgeon General US Department of Health Education and Welfare Washington D C 1971

Ibid 1972

Ibid 1973

Ibid 1974

Ibid 1975

Swedish Central Bureau f Statistics Smoking habits in Sweden Stockholm 1965 (in Swedish)

Takkunen J Anthropometric electrocardiographic and blood pressure tudies on adult male twins Ann Acad Sci Fenn (Med) 107 1964

Thomas C B Familial and epidemiologi aspects of coronary disease and hypertension J Chron Dis 7 198-208 1958

Tibblin G Primary and secondary risk factors Läkartidn 69 4645-4647 1972 (in Swedish)

Tokuhata G K Famili l factors in human lung cancer and smoking Amer J Publi Health 54 24 32 1964

Twi registries in the study of chronic disease Acta Med Scand suppl 523 1971

US Dept HEW Mortality by industry and cause of death among men 20 to 64 years f age Vital Statistics Special Reports Vol 53 No 4 1963

Vandenberg S G Twin studies In Human behavior genetics Ed A R Kaplan C C Thomas Springfield Ill 1976

Webb D R Condemi J J Selective immunoglobulin deficiency and chroni obstructive lung disease A family study Ann Intern Med 80:618-621 1974

Werkö L, Risk factors and coronary heart disease facts or fancy? Amer Heart J 91 87-98 1976

Nikkilä E A Aro A Family study of serum lipids and lipoproteins in coronary heart disease Lancet 1:954-958 1973

Osborne R H Adlersberg D de George F V Wang C Serum lipids heredity and environment A study of adult twins *Amer J Med 26:54 59 1959*

Ostfeld A M Lebovits B Z Shekelle R B Paul O A prospective study of the relationship between personality and coronary heart disease J Chron Dis 17:265-276 1964

Partanen J Bruun K Markkanen T Inheritance of drinking behavior A study on intelligence personality and use of alcohol of adult twins Almqvist and Wiksell Stockholm 1966

Rose G The diagnosis of ischaemic heart pain and intermittent claudication in field surveys Bull World Health Organ 27 645-658 1962

Rose G Chest pain questionnaire Milbank Mem Fund Q 43:32 39 1965

Royal College of Physicians Smoking and health Pitman Medical and Scientific Publishing Company Ltd London 1962

Royal College of Physicians Smoking and health now Pitman Medical and Scientific Publishing Company Ltd London 1971

Russek H I Zohman B L Relative significance of heredity diet and occupational stress in coronary heart disease of young adults Amer J Med Sci 235 266-277 1958

Schubert D S P College smoking and personality profiles Amer Psychol 13:322 1958

Schwartz M Heredity in bronchial asthma Acta Allerg 5 suppl 2 1952

Selltiz C Jahoda M Deutsch M Cook S W Research methods in social relations Holt Rinehard and Winston New York 1966

Seltzer C C Bosse R Garvey A J Mail survey respons by smoking status Amer J Epidemiol 100:453-457 1975

Seltzer C C Friedman G D Siegelaub A B Smoking and drug consumption *in white black and oriental men and women Amer J Ph 64 466-473* 1974

Seltzer C C Friedman G D Siegelaub A B Collen M F Smoking habits and pain tolerance Arch Environ Health 29 170-172 1974

Shields J Monozygotic twins brought up apart and brought up together Oxford University Press London 1962

Silverberg E Hollab A I Cancer statistics 1973 CA 23 1-27 1973

Smith C Concordance in twins Methods and interpretation Amer J Hum Genet 26 454-466 1974

Smith R T A comparison of socio-environmental factors in monozygotic and dizygotic twins testing an assumption In Methods and goals in human behavioral genetics Ed S G Vandenberg Academic Pre s New York 1965

WHO Technical meeting Copenhagen 6-8 May 1963 Survey of the prevalence of ischaemic heart disease in certain European countries Euro 179 3 (Pr) 1963

WHO The use of twins in epidemiological studies Report of a WHO meeting of investigators World Health Organ Chron 20 121 1966

WHO International classification of disease 1965 revision Geneva 1967

WHO Expert committee on smoking and its effects on health Technical report series 568 Geneva 1975

Winzeler M Braun P Grob P J Familiär gehäufte Bronchiektasen und alfa$_1$-Antitrypsin-Mangel Schweiz Med Wochenschr 104 1705-1711 1974

Wynder E L Etiology of lung cancer Reflections on two decades of research Cancer 30 1332-1339 1972

Östlyngen E Possibilities and limitations of twin research as a means of solving problems of heredity and environment Acta Psychol 6:59-90 1949

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Medical, occupational and smoking characteristics related to ischemic heart disease in men and women

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By Heikki Juustila

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

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Supplementum 613

Medical, occupational and smoking characteristics related to ischemic heart disease in men and women

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By Heikki Juustila

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

From the Department of Medicine University of Oulu Finland

(Head Professor W J Kaipainen M D)

MEDICAL OCCUPATIONAL AND SMOKING CHARACTERISTICS RELATED TO ISCHEMIC HEART DISEASE IN MEN AND WOMEN

Field survey of age group 40 59 in a rural population at Haapavesi Northern Finland

By

Heikki Juustila

Oulu, 1977

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cholesterol as a risk factor of IHD

olesterol is one of the most thoroughly investigated risk factors included in all comprehensive works on the epidemiology in IHD lowing data on cholesterol have been recorded in USA (Serum rol levels of adults National Center for Health Statistics The cholesterol level increases in both men and women until ately the age of 40 In men older than that the increase then f at a cholesterol value of appr 230 mg/100 ml In women the ontinues linearly until the age of 60 when the level is appr ml In USA 23 % of the men aged 35 64 have a cholesterol 59 mg/100 ml while a corresponding value among the women ined for 12 9 % of those aged 35 44 28 % of those aged 49 7 % of those aged 55 64

gham Study (Kannel et al 1961) showed that the men aged cholesterol value exceeded 244 mg/100 ml had a 3 4 times dence than the men whose cholesterol value was below The corresponding risk for women was 2 4 times higher of the same study it has been concluded that the t in question the more significant is the cholesterol disease In women aged over 50 the serum cholesterol icance for coronary disease (Kannel et al 1966) rt in the same study (Kannel et al 1971 a and b) rum cholesterol level is the risk factor most incidence of coronary disease When the cholester ml the ratio between observed and expected but when the cholesterol level was 300 mg/ of threefold These data pertain to men

CONTENTS

In several mass surveys the term ischemic heart disease has been replaced by the term coronary heart disease (CHD) In practice these two terms generally mean the same For the present purposes the term ischemic heart disease was chosen as it refers to verified ischemia of the cardiac muscle regardless of the state of the coronary arteries or the symptoms of the subjects The term coronary heart disease includes pathologico-anatomical changes in the coronary arteries which are severe enough to bring about a cardiac disease (Hurst 1974) In the following text however the term coronary heart disease has been used when refering to previous investigations

According to the studies of Karvonen et al (1967 and 1970) the incidence and prognosis of IHD exhibit distinct regional differences in Finland This observation is supported by the investigations of Rissanen (1972) and possibly also by the pathologico-anatomical investigations of children carried out by Pesonen et al (1975) though the latter studies did not directly pertain to IHD The nature of IHD in each locality and the effect of risk factors on morbidity can be determined by well directed mass screening surveys Thereby some basis is obtained for possible preventive measures

Fo the above reasons it was considered expedient to conduct a mass screening survey in a typical northern Finnish municipality with a public health staff actively interested in such an investigation A high percentage of participation could be expected which is one of the most important conditions for a successful realization of a project of this kind Examination of women in comparison with men was also deemed important because several previous mass screening surveys had pertained to men

The following risk factors of IHD were investigated serum cholesterol and triglycerides systolic and diastolic blood pressure reduced glucose

INTRODUCTION

Finnish men have the highest mortality from ischemic heart disease (IHD) in the world (WHO 1967 and 1972 Miettinen 1969 and 1971 Pyörälä 1974) The cardiac mortality rate of Finnish women is also among the highest in the world (Epstein and Krueger 1969) being the highest in Scandinavia (Bolander 1971)

In addition to using statistics on the causes of death the occur rence of IHD can be investigated by mass surveys of the prevalence and incidence of IHD and the relationship of IHD to certain risk factors

There are mass surveys in progress in different parts of the world they began as prevalence studies and continue as follow-up studies including repeated investigation of the subjects after a certain period which gives information on the incidence of IHD (Dawber et al 1957 Kannel et al 1962 Epstein et al 1965 Tibblin 1969 Welborn et al 1969)

Most of the mass surveys have been carried out on men while less interest has been directed to women Recently however women have also been included among the series investigated (Bengtsson 1973 a Bengtsson et al 1973 b Hagerup 1973)

The best known among the Finnish mass surveys is the east west study (Karvonen et al 1967 Keys 1967 and 1970) which dealt with mid dle-aged men There is also a Finnish investigation being carried out which pertains to both men and women and also covers localities in Northern Finland (Pyörälä et al 1973 Reunanen et al 1973) Compre- hensive studies of the return to work by myocardial infarction patients (Vuopala 1972) and their rehabilitation (Palatsi 1976) have also been made in Northern Finland Yet the data on the epidemiology of IHD

have so far been insufficient

Serum cholesterol as a risk factor of IHD

Cholesterol is one of the most thoroughly investigated risk factors and is included in all comprehensive works on the epidemiology in IHD The following data on cholesterol have been recorded in USA (Serum cholesterol levels of adults National Center for Health Statistics 1967) The cholesterol level increases in both men and women until approximately the age of 40 In men older than that the increase then levels off at a cholesterol value of appr 230 mg/100 ml In women the increase continues linearly until the age of 60 when the level is appr 260 mg/100 ml In USA 23 % of the men aged 35 64 have a cholesterol level over 259 mg/100 ml while a corresponding value among the women has been obtained for 12 9 % of those aged 35 44 28 % of those aged 45 54 and 49 7 % of those aged 55 64

The Framingham Study (Kannel et al 1961) showed that the men aged 40 59 whose cholesterol value exceeded 244 mg/100 ml had a 3 4 times higher CHD incidence than the men whose cholesterol value was below 210 mg/100 ml The corresponding risk for women was 2 4 times higher

On the basis of the same study it has been concluded that the younger the subject in question the more significant is the cholesterol level for coronary disease In women aged over 50 the serum cholesterol level has no significance for coronary disease (Kannel et al 1966)

The 16-year report in the same study (Kannel et al 1971 a and b) furthe shows that serum cholesterol level is the risk factor most clearly affecting the incidence of coronary disease When the cholester ol level was 200 mg/100 ml the ratio between observed and expected cases of new CHD was 0 7 but when the cholesterol level was 300 mg/ 100 ml this ratio was 2 1 of threefold These data pertain to men

tolerance obesity and overweight smoking and occupation The relationship of each risk factor to IHD was examined using certain ECG changes as the criteria of IHD

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aged 30 - 49

These are even more recent data on the Framingham series (Kannel and Castelli 1972) which show that high cholesterol values are associated with an increased risk of CHD in women aged below 50 just as they are in men In women aged over 50 however triglycerides are a more significant risk factor

On the basis of the Framingham findings Epstein (1967 b) predicted that 27 % of the men whose cholesterol level exceeded 260 mg/100 ml would develop coronary disease within 10 years

The Albany study (Doyle et al 1959) of men aged 39 - 55 showed that the subjects with cholesterol below 200 mg/100 ml have an annual CHD incidence of 6 0/1000 ml while those with a cholesterol level higher than 275 mg/100 ml have a threefold CHD incidence or 19 0/1000

In their work carried out in Minnesota Keys et al (1963) noted that the men aged 45 - 55 whose cholesterol exceeded 269 mg/100 ml had a 5 5 times higher CHD incidence than those whose cholesterol was below 200 mg/100 ml In Evans County Georgia (McDonough et al 1965) the CHD prevalence was 2 2 times higher among the white men aged 40 74 whose cholesterol exceeded 250 mg/100 ml than among those whose cholesterolwas below that value

An investigation of white men in Los Angeles (Chapman and Massey 1964) revealed a 4 5 times higher frequency of myocardial infarction in those whose cholesterol was in the range 270 - 389 mg/100 ml than in those whose cholesterol was below 210 mg/100 ml Subsequent results of the same investigation (Chapman et al 1971) show that the incidence of myocardial infarction becomes twofold in the cholesterol group of 270 - 389 mg/100 ml compared with the group below 210 /100 ml The dependence between cholesterol and coronary disease has also been noted

The Busselton study carried out in Australia (Welborn et al 1969) showed that serum cholesterol elevated blood pressure and declined glucose tolerance were all significantly and independently of each other associated with coronary disease in both sexes the risk ratio for each approximately twofold

The London study conducted by Morris et al (1966) revealed nearly 4 times more new cases of CHD in the highest cholesterol quintile than in the lowest quintile over a follow-up period of 5 years

In a follow-up study of men in Oslo (Westlund and Nicolaysen 1966) the incidence of new coronary cases was 40 2/1000/year among those with a cholesterol value over 400 mg/100 ml but only 2 6/1000/year among those whose cholesterol value was below 200 mg/100 ml

The Stockholm study by Carlson and Böttinger (1972) revealed a very low frequency of coronary disease but there was still a correlation between cholesterol and the incidence of coronary disease In the Gothenburg study (Bengtsson et al 1973 a) on women on the other hand the cholesterol values of a myocardial infarction group an angina pectoris group and a coronary ECG group did not differ from the control values

The Finnish east-west investigation (Karvonen et al 1970) revealed a clear correlation between cholesterol on the one hand and myocardial infarction and sudden deaths on the other over a follow-up period of 5 years The risk was 4 times higher in the highest quintile than in the lowest

In this review Stamler (1973) concludes that as the cholesterol level rises the risk for atherosclerosis disease increases and that this dependence appears in all age groups at least from young adult hood through middle age According to Stamler a cholesterol value below 200 mg/100 ml is normal 200 249 mg/100 ml is border line and 250 mg/100 ml is pathological for Americans aged over 30 He

further postulates that people with a cholesterol value over 250 mg/100 ml have a twofold risk of developing premature coronary heart disease compared with those with a cholesterol value below that limit Summarizing the research on coronary disease and cholesterol Stamler maintains that the serum cholesterol level is the best simple measure for estimating the risk of atherosclerotic disease particularly coronary disease

In Ireland Mulcahy et al (1969) investigated 400 men aged under 60 suffering from coronary disease finding high cholesterol declined glucose tolerance hypertension and smoking to be risk factors of CHD

Nikkilä (1972) points out that the risk for coronary disease correlates strongly with the serum cholesterol level and becomes 3- to 5 fold within the range 200 - 300 mg/100 ml The probability of coronary disease increases progressively the more the higher the cholesterol level but the correlation apparently weakens beyond the age of 60

Both cross-sectional and longitudinal studies have hence given rise to quite a unanimous agreement that serum cholesterol is a significant risk factor of IHD for both sexes at least in younger and middle age while women over 50 no longer display any clear correlation

Serum triglycerides as a risk factor of IHD

The information available on triglycerides as a risk factor IHD is markedly less abundant than that on cholesterol because triglyceride assays were included in the mass investigations later than the cholesterol assays

According to he most recent Framingham reports (Kannel and Castelli 1972) triglycerides are a more significant risk factor than cholesterol in women over 50 while in women aged under 50 cholesterol is more important as it also is in men within all the age classes studied (30

62 years)

Of the other studies made in USA at least the investigation conducted by Brown (1969) and Rosenman et al (1970) revealed a correlation between triglycerides and IHD

In Carlson and Böttinger s study (1972) in which over 3000 men were followed up for 9 years the frequency of IHD (myocardial infarctions + sudden deaths) increased linearly along with the rise of triglyceride and cholesterol levels The authors point out that plasma triglycerides and cholesterol are risk factors for IHD independent of each other and a combined elevation of these two plasma lipids carries the highest risk for IHD"

The Gothenburg study of women (Bengtsson et al 1973 a) revealed a significantly higher triglyceride level in the women with myocardial infarction and those with coronary ECG than in the control group The women with angina pectoris however had no difference in triglycerides compared with the control group

Nitter-Hauge and Enge (1973) performed selective coronary angiography on 71 patients of whom 46 had had myocardial infarction and 25 had angina pectoris This work established no correlation between the degree of obstruction of the coronary vessels and serum triglycerides or cholesterol

In this review Stamler (1973) discusses his own epidemiological studies stating thus Fasting serum triglycerides are not superior predictors of risk Earlier claims of this kind based on preliminary or unsatisfactory data have not withstood the test of time

In the survey of policemen carried out by Pyörälä et al (1976) triglycerides correlated with the risk of myocardial infarction together with systolic and diastolic hypertension plasma cholesterol relative weight and smoking over the 5-year follow-up but in a multivariate analysis triglycerides and diastolic hypertension were elimi

nated from among the risk factors The combination of high cholestero and high triglycerides turned out as a prominent factor for the risk o myocardial infarction even in that work

The significance of triglycerides as an independent risk factor of IHD so far remains unclear but there is probably no doubt that a high triglyceride level combined with high cholesterol correlates stron with ischemic heart disease

Hypertonia as a risk factor of IHD

The correlation between hypertonia and IHD has been studied widely especially in men the corresponding data for women being much less frequent

It is unanimously agreed at the present time that systolic and diastolic blood pressure are risk factors of IHD (Kannel et al 1961 Epstein 1965 Stamler et al 1966 Paul 1971 Gordon and Kannel 1972)

According to the Framingham study the incidence of atherosclerotic heart disease in men with blood pressures ranging within 140/90 160/95 was 2 4-fold compared with the average over a follow-up period of 4 years (Opstad 1966)

According to the same study (Kannel et al 1961) the 40- to 59 year old men in the upper 5 per cent level of blood pressure had a 2 6 fold CHD incidence compared with the population at risk while the women of the same age had a 6 fold risk

According to an early Tecumseh report (Epstein et al 1965) elevated blood pressure is clearly associated with increased CHD prevalence

The western collaborative study (Rosenman et al 1966) showed the CHD incidence to be 3 6 times higher in the subjects with a diastolic blood pressure over 94 mmHg than in those with a diastolic pressure below that value

In the Evans County study (McDonough et al 1965) the CHD prevalence was 2 3 times higher in the subjects whose blood pressure exceeded 160/90 than in those with lower values

Cotton et al (1972) compared 91 men aged under 65 suffering from coronary disease and 98 healthy men finding out that the following factors dominated in the coronary patients diastolic hypertension arcus baldness xanthelasma a family history of hypertension past smoking habits and hyperlipemia Of these factors diastolic hypertension emerged as much the most important

Mulcahy et al (1967) examined 100 women with coronary disease (35 had angina pectoris 21 acute coronary insufficiency and 44 myocardial infarction) Hypertension cigarette smoking and hypercholesterolemia were found to be risk factors cigarette smoking and hypertonia were recorded together or separately for 80 90 % of the patients These findings gave rise to the conclusion that correct control of hypertension and cessation of smoking could reduce even dramatically the CHD incidence in middle-aged women

According to Stamler (1964) both morbidity in myocardial infarction and coronary mortality correlate with diastolic hypertension In the work on DuPont employees (Pell and D Alonzo 1961) hypertonic subjects were also found to have an increased frequency of myocardial infarctions According to the data of the Health Insurance Plan of Greater New York (HIP) (Weinblatt et al 1968) both mortality from myocardial infarction and recidivous infarctions were more common among hypertonic subjects than among normotensive ones Chapman and Massey (1964) however noted no correlation between myocardial infarction and elevated blood pressure in their follow-up study of men aged below 60 A study based on the autopsy material of the International Atherosclerosis Project (McGill 1968) on the other hand revealed a significant correlation between hypertension and the severity of atherosclerosis

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In the Busselton study carried out in Australia (Welborn et al 1969) hypertension was found to be a risk factor of CHD in both men and women The study of women by Swedish Bengtsson (1973 b) revealed significantly more cases with hypertonia and a family history of hypertension in the group with myocardial infarction than in the control group

In the Finnish east west study (Karvonen et al 1970) hypertonia was found to correlate with CHD incidence in men aged 40 - 59 years over a follow-up period of 5 years

Simborg (1970) states that even mild hypertonia is associated with increased CHD incidence He further points out that hypertonia can now be treated effectively but it is not known whether the treatment has any reducing effect on CHD incidence

Stamler (1973) similarly establishes hypertonia as a risk factor of CHD independent of other risk factors e g hypercholesterolemia or smoking

Kannel (1974) concludes from his findings that hypertonia is the most general and potent contributor to cardiovascular mortality among all the risk factors He also states that elevated pressure casual or basal labile or fixed systolic or diastolic at any age in either sex is a potent contributor to all forms of cardiovascular disease

According to the current investigations both systolic and diastolic hypertension are thus among the most potent risk factors in both sexes

Diabetes mellitus and glucose intolerance as risk factors of IHD

The reports on the prevalence of clinical coronary disease in diabetics vary from 26 to 42 % (Ostrander et al 1965 b Lal and Bahl 1967) These studies reveal the significant feature that IHD is common in both female and male diabetics

Herman and Gorlin (1965) noted that studies among persons with unexplained or premature coronary artery disease reveal an unusually high number with preclinical diabetes Autopsy studies of diabetics show significant coronary disease in 75 89 % of cases (Stears et al 1947 Marble 1955)

According to some investigations people with atherosclerotic disease have reduced glucose tolerance more often than the controls (Inter society commission for heart disease resources 1970 Stamler 1967 Stamler et al 1972 Stamler and Epstein 1972)

Stamler et al (1960) found the occurrence rate (prevalence and incidence) of CHD to be twice as high in diabetics as in nondiabetics

According to the Framingham study (Kannel et al 1967 a) the CHD incidence was 1 4 times as high in diabetics as in nondiabetics among the 30- to 59-year old men with no signs of CHD at the beginning of the study The corresponding risk of female diabetics was 2 5-fold The risk of death from CHD was 2 3 times higher in diabetic men and 5 7 times higher in diabetic women

The Tecumseh study (Stamler and Epstein 1972) showed that asymptomatic hyperglycemia correlated with CHD prevalence in both men and women and was independent of e g cholesterol and hypertonia CHD incidence was also found to correlate with hyperglycemia

In the study of DuPont Company (Stamler 1967 Stamler et al 1972 Stamler and Epstein 1972) which covered 73000 women and men aged 25 64 clinical diabetes was found to be an independent risk factor of CHD

In the study of Peoples Gas Company in Chicago (Stamler et al 1972) it was found out that during 1965 1970 mortality from coronary disease was 42/1000 among hyperglycemic subjects and 16/1000 among normoglycemic ones The same study also revealed a correlation between hyperglycemia and hypertonia the higher the blood sugar content was after an hour s loading the higher were the systolic and diastolic blood pressure val

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Krotkiewski et al (1970) examined 61 diabetics (38 men 23 women age 19 49 yr) without any sign of cardiovascular disease in Warsaw Mater s step test showed ST/T changes suggestive of latent coronary disease in 19 6 % of the patients (women 30 4 % men 13 1 %) No dif ferences connected with the age of the patients the duration of dia betes or the therapy given for it were seen

Ostrovskaya-Tsarfis et al (1972) examined 5107 middle-aged men from the Moscow area for diminished glucose tolerance and noted that the incidence of disturbed tolerance to carbohydrates was 43 6 % including diabetes mellitus 3 5 % The incidence is statistically significantly associated with the level of cholesterol and not associated with the level of triglycerides and total lipids of the blood serum Disturbed tolerance to carbohydrates in middle-aged men is one of the independent factors of the risk for the ischemic disease of the heart The signifi cance of this factor grows when it is combined with marked hypercholester olaemia

In the Australian Busselton study (Welborn et al 1969) high serum cholesterol elevated blood pressure and diminished glucose tolerance were significantly and independently of each other associated with coro- nary disease in both sexes the risk was about twofold

In the investigation carried out by Bengtsson et al (1973 c) a group with myocardial infarction turned out to have significantly more manifest diabetes than the control group No corresponding difference appeared in the angina pectoris group or the group with pathological ECG Nor did an i v glucose injection reveal any significant dif ferences between the different groups This investigation pertained to women

Epstein (1967 a) postulates that there is a correlation between hyperglycemia and myocardial infarction hyperglycemia is somehow as sociated with hyperlipemia positive calorie balance hypertonia and

smoking but it remains to be elucidated whether hyperglycemia is an independent risk factor of IHD

In his cross sectional study of policemen in Helsinki Lehtovirta (1973) noted that both manifest diabetes and reduced glucose tolerance are closely correlated with obesity The same phenomenon was discussed by Miettinen (1971) who pointed out that adult age diabetes correlates with obesity and hypertriglyceridemia

In the 5-year follow-up of the Helsinki policemen (Pyörälä et al 1976) neither diabetes nor reduced glucose tolerance emerged as independent risk factors or as risk factors of myocardial infarction in a multivariate analysis

Manifest diabetes is hence generally considered a risk factor of IHD while the significance or reduced glucose tolerance as an independent risk factor varies in both cross sectional and longitudinal studies In any case diabetes and reduced glucose tolerance correlate with obesity and hyperlipidemia which combination in turn is a significant risk factor of IHD

Overweight and obesity as risk factors of IHD

The relationship of overweight and obesity to ischemic heart disease has been investigated in several mass surveys

In an early Framingham report (Dawber et al 1957) a correlation between obesity and atherosclerotic heart disease was noted in men aged 45 62

In another early report of the same investigation (Kannel et al 1962) an increased CHD incidence was associated with cases where over weight exceeded 30 % but not with those where the percentage was smaller Of the risk factors examined obesity had the poorest correlation with coronary disease

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The Australian Busselton study (Welborn et al 1969) revealed no significant correlation between obesity and coronary disease in either sex

The studies by Keys et al (1972) showed a clearly increased incidence of coronary disease relative to overweight and obesity in men aged 40 59 in USA and Southern Europe but not in Northern Europe The multivariate analysis of the same study showed that neither relative nor obesity were independent risk factors of imminent CHD when age blood pressure cholesterol and smoking were comparable Relative weight and obesity correlated with blood pressure and serum cholesterol Their correlation with smoking was negative the smokers were thinner than the non-smokers This investigation also included Finnish men (the East West study)

In the investigation of policemen aged 30 59 in Helsinki conducted by Pyörälä et al (1976) obesity had a prognostic value for the risk of myocardial infarction independent of blood pressure and blood lipids this finding was made in the older age-groups but not in the younger The multivariate analysis of the same study established smoking systolic hypertension and plasma cholesterol along with relative weight as risk factors of myocardial infarction.

Miettinen (1971) maintains in his review of diabetes that if obesity is associated with diabetes of adult onset concurrent hypertriglyceridemia is very common It has also been noted that the plasma insulin content of obese subjects is often increased although their glucose tolerance may be normal (Nikkilä et al 1965 Chiles & Tzagournis 1970)

Both cross sectional and longitudinal studies have thus shown correlations between overweight and obesity on the one hand and different

According to two subsequent Framingham reports (Dawber et al 1963 Kannel et al 1967 b) CHD incidence increases along with overweight but no correlation between overweight and myocardial infarction was noted in any age class of either sex Angina pectoris and overweight however have a strong positive relationship in both men and women Furthermore overweight was found to correlate with sudden deaths due to arrythmias

In his extensive survey Simborg (1970) postulates that there is a weak correlation between overweight and total CHD incidence but that no correlation probably exists between overweight and myocardial infarction or overweight and sudden deaths due to myocardial infarction Obesity predisposes to angina and sudden death from arrythmia but does not predispose to myocardial infarction

In the Tecumseh study (Epstein et al 1965) a 1 7 fold CHD inci dence was noted among those in the uppermost quintile of relative weigh compared with the other men or women

In their prospective study Stamler et al (1960) noted a twofold CHD incidence in the subjects whose relative weight exceeded 113 compar with those who had a corresponding value below 100 In that study CHD included myocardial infarction sudden death coronary insufficiency and congestive cardiac insufficiency due to coronary disease

The investigation of businessmen in Los Angeles (Chapman and Massey 1964) on the other hand revealed no correlation between overweight and CHD during a 16 year follow-up

A similar result was also obtained in a corresponding study carried out in Chicago (Paul et al 1963) These investigators also measured the thickness of skinfolds which correlated positively with CHD inci dence Both of these works included myocardial infarction and angina pectoris under the label of CHD

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Both cross sectional and longitudinal studies have thus shown correlations between overweight and obesity on the one hand and different

manifestations of IHD on the other but the findings are somewhat con dictory The greatest significance of obesity as a risk factor of IH probably lies in the fact that it is closely associated with hyperton hyperlipidemia and diabetes

Smoking as a risk factor of IHD

Cigarette smoking has turned out to be a significant risk factor of IHD particularly in young and middle-aged men (Doll and Hill 1964 Doyle et al 1964 Frank et al 1966 Hammond 1966 Hill and Wynder 1974) The cross-sectional studies at Tecumseh USA (Epstein et al 1965) and Busselton Australia (Welborn et al 1969) established no correlation between smoking and angina pectoris or ischemic ECG change and the cross-sectional findings at Framingham also showed that angina pectoris is no more common among smokers than non smokers (Dawber et al 1957) The correlation between smoking and IHD generally appears clearly in longitudinal studies only In the National Co-operative Pooling Project a follow-up study of men aged 30 59 showed that cigarettes rendered the incidence of myocardial infarction twofold independently of the other risk factors the risk of sudden death was found to be 1 9 fold for those who smoked 10 cigarettes daily 3 4 fold for those who smoked over 20 cigarettes daily (Inter Society Commission for Heart Disease Resources 1970)

Cigarette smokers also have a shorter life-time after the appearance of coronary symptoms than non smokers and those who give up smoking have a lower incidence of myocardial infarction and death from CHD than those who continue smoking (Spain and Bradess 1970)

Several follow-up studies (e g Morris et al 1966 Tibblin and Wilhelmsen 1970) have shown that cigarette smokers have a higher CHD incidence than non-smokers

Rose (1976) estimated that the men who smoke 15 cigarettes daily have a twofold CHD risk compared with non-smokers and the risk of those who smoke 40 cigarettes is a 12 5-fold

Cigarette smoking has been found to increase the incidence of angina pectoris in some studies (e g Shapiro et al 1969) while in some others the incidence of angina pectoris does not correlate with cigarette smoking (e g Tibblin and Wilhelmsen 1970) Cigarette smoking has been found to diminish the exercise tolerance of angina pectoris patients (Aronow et al 1968 Aronow and Rokaw 1971 Aronow and Swanson 1969 a) Cigarettes with a high nicotin content give rise to chest pain during exercise more easily than cigarettes with a low nicotin content (Aronow et al 1968) which in turn produce chest pain upon exercise in angina pectoris patients more easily than cigarettes containing no nicotin (Aronow and Swanson 1969 b)

The cross sectional study of nearly 20000 middle-aged (40 64 yr) British men carried out by Reid et al (1976) showed a positive correlation for angina pectoris and anamnestic myocardial infarction on the one hand and smoking on the other and this association was independent of e g high cholesterol or hypertension The follow-up of this series (5 yr) revealed a correlation between smoking and coronary mortality which was also independent of other risk facotrs

The Framingham Study showed (Inter Society Commission for Heart Disease Resources 1970) that if abundant cigarette smoking (20 cigarettes/day) was accompanied by high cholesterol (over 7 8 ml/l) and elevated diastolic blood pressure (over 105 mmHg) the risk of myocardial infarction or CHD death became 8 5-fold over the 10-year follow-up Several other surveys (e g Wilhelmsen et al 1973) have also indicated that the combination of hypertension high cholesterol and cigarette smoking among men are highly prognostic of myocardial infarction and sudden death

Werkö (1976) points out in his review that if smoking is associated with high cholesterol or high blood pressure or both the risk of coronary death becomes about fourfold At the same time Werkö makes the conclusion that no single risk factor is of any greater importance by itself

The Framingham report on smoking after 18-year follow-up (Gordon et al 1974) shows that non-smokers pipe- or cigar-smokers and those who smoked 10 cigarettes or less daily had lower CHD mortality than those who smoked more than 10 cigarettes daily This finding applied to men The men who smoked at the beginning of the investigation but then gave up smoking had only a half of the number of CHD attacks suffered by the men who went on smoking

In her follow-up study made in Norway (about 8000 middle-aged women and 7000 men) Zeiner-Henriksen (1976) examined the relationship between CHD mortality and smoking over 6 years The highest mortality was recorded for the cigarette-smoking men and the mixed smokers (both cigarettes and pipe) in both urban and rural populations It was also noted that rural men had the same CHD mortality regardless of whether they smoked pipe/cigar or cigarettes Some other investigations have also shown a positive correlation between CHD mortality or incidence and pipe/cigar smoking (Inter Society Commission for Heart Disease Resources 1970 Shapiro et al 1969)

The same study by Zeiner Henriksen revealed equal CHD mortality among female non-smokers and smokers in both urban and rural populations

Bengtsson (1973 d) found no differences in smoking among women with *angina pectoris* and women with coronary ECG The group of women with myocardial infarction however contained significantly more smokers than non smokers

The east-west study showed CHD mortality to be considerably higher among both ex smokers and smokers than male non-smokers (Punsar and Pyörälä 1971 Punsar 1970)

Ball and Turner (1974) point out that 52000 Britons die annually for causes directly dependent on smoking and that about half of these deaths are due to cardiovascular diseases mainly CHD Of the consumption of cigarettes were reduced by 20 % there would be 8000 deaths fewer in 1984 This would reduce the number of coronary deaths more than any other method known

Karvonen estimated (1972) that 1000-1800 working age men die a coronary death in Finland every year owing to cigarette smoking

The correlation between cigarette smoking and IHD is uncertain in cross-sectional studies while longitudinal studies have conclusively shown cigarette smoking to increase the sudden deaths of men due to coronary disease Smoking also increases the CHD incidence among men though the effect of smoking on angina pectoris remains open to speculation It seems however that smoking reduced the exercise tolerance of ancina pectoris patients There is also some evidence indicating that pipe/cigar smoking would similarly correlate with CHD mortality among men As regards women there is not yet sufficient evidence of any correlation between CHD and smoking

The combination of smoking hypertension and high cholesterol in men has been found to be the most serious risk factor of myocardial infarction and sudden coronary deaths

Occupation as a risk factor of IHD

There is not much literature dealing with the correlation between IHD and occupation There are however several studies on IHD and physical activity and inactivity involved in the occupation Most of these studies have shown higher CHD mortality and incidence in inactive

Werkö (1976) points out in his review that if smoking is associated with high cholesterol or high blood pressure or both the risk of coronary death becomes about fourfold At the same time Werkö makes the conclusion that no single risk factor is of any greater importance by itself

The Framingham report on smoking after 18 year follow up (Gordon et al 1974) shows that non-smokers pipe- or cigar-smokers and those who smoked 10 cigarettes or less daily had lower CHD mortality than those who smoked more than 10 cigarettes daily This finding applied to men The men who smoked at the beginning of the investigation but then gave up smoking had only a half of the number of CHD attacks suf fered by the men who went on smoking

In her follow-up study made in Norway (about 8000 middle-aged women and 7000 men) Zeiner Henriksen (1976) examined the relationship between CHD mortality and smoking over 6 years The highest mortality was recorded for the cigarette-smoking men and the mixed smokers (both ciga rettes and pipe) in both urban and rural populations It was also noted that rural men had the same CHD mortality regardless of whether they smoked pipe/cigar or cigarettes Some other investigations have also shown a positive correlation between CHD mortality or incidence and pipe/cigar smoking (Inter Society Commission for Heart Disease Resources 1970 Shapiro et al 1969)

The same study by Zeiner-Henriksen revealed equal CHD mortality among female non smokers and smokers in both urban and rural populations

Bengtsson (1973 d) found no differences in smoking among women with angina pectoris and women with coronary ECG The group of women with myocardial infarction however contained significantly more smokers than non-smokers

Karvonen et al (1972) noted a higher CHD incidence among the lumber jacks in Ilomantsi than the other men of the same locality over a follow-up period of 10 years

Pyörälä (1972) examined the association between CHD and physical activity on the basis of epidemiological investigations made in different parts of the world In these works physical activity has frequently been expressed in terms of occupation Pyörälä concludes that physical inac tivity is accompanied by an increased risk of coronary disease Accord ing to him this risk is independent of other risk factors such as hy pertension cholesterol level or obesity

So far the correlation between IHD and occupation is vague for both sexes Some studies have shown that agricultural workers have less coro-nary disease than people doing lighter work Finnish lumberjacks how ever were found to have a higher CHD incidence than the other men cov ered in the investigations

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In a survey of kibbutz workers in Israel (Brunner & Manelis 1971) agricultural workers were found to have a lower CHD incidence than ones doing light work this applied to both women and men The same results also showed than agricultural workers had a lower incidence of angina pectoris myocardial infarction and coronary deaths than people with light jobs

The Evans County Study (Cassell et al 1971) showed that agricul tural workers had a CHD incidence which was only about half of the corresponding incidence of people holding other occupations and they were also found to have lower CHD mortality

Zeiner Henriksen (1976) examined CHD mortality in different occu pational groups 1) workers in agriculture or forestry and fishermen 2) workers in commerce and industry and service occupations 3) of ficials administrators etc The investigation covered about 7000 men and 8000 women During the follow-up of six years CHD mortality was highest in group 2 and lowest in group 1 It was possible that the people in group 1 had the most active occupation physically This finding pertained to men no corresponding result for women is reported

Bengtsson (1973 c) found a correlation between physically inactive occupation and myocardial infarction in a female series including 47 women who had suffered a myocardial infarction He did not note any significant difference in socioeconomic status between the IHD women and the control women (Bengtsson 1973 e)

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MATERIAL

The investigation was carried out at Haapavesi which is a typical Northern Finnish municipality It is located in Northern Ostrobothnia appr 140 km south of Oulu In 1971 when the investigation was made there were about 7500 inhabitants at Haapavesi with 50 60 % working in agriculture and forestry and fairly equal portions of the remaining group in commerce transportation and services

The project was carried out during five weeks in April May 1971 The examinations were made in the Haapavesi Local Hospital All the men and women living at Haapavesi who were 40 59 years old according to the census list made on Jan 1 1970 were invited to the examination by a personal letter Altogether 1686 invitations were sent

The census list for 1971 which was completed immediately after the beginning of the investigation showed that 36 of those invited had either died or moved away from Haapavesi during 1970 Conversely 60 people had moved there and 24 of them came to be examined

Thus there were altogether 1710 people aged 40 59 at Haapavesi at the time of the investigation and 1554 of them participated in it The percentage of participation was hence 90 9 % 793 women and 761 men were examined

The series of subjects is described in greater detail in the chapter on results and in the discussion

PURPOSE OF THE PRESENT STUDY

The purpose was

- to study the prevalence of IHD among middle aged rural men and women
  to examine the correlation of certain risk factors as well as smoking and occupation to IHD
- to find out whether the men and women differ from each other in the occurrence and significance of these factors

METHODS

Laboratory studies

The subjects came to be examined after 12 15 hours fasting First a venous blood sample was drawn for cholesterol and triglyceride assays (Pearson et al 1953 Royer and Howard 1969) and a capillary blood sample for a determination of blood sugar (Hyvärinen and Nikkilä 1962) Immediately thereafter the subjects were given sugar solution (Glukodyn[R]) 1 g/kg and after two hours a new capillary blood sample was drawn for determining the 2 hour blood sugar

The blood sugar assays were made immediately in the laboratory of the local hospital the cholesterol and triglyceride measurements were performed later on deep-frozen sera in the laboratory of the Oulu Deaconess Institute

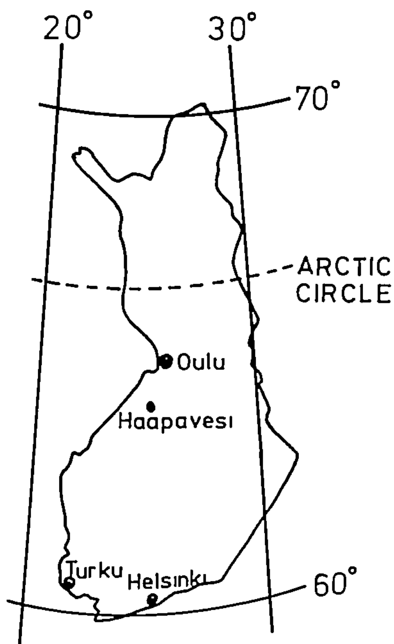
Anthropomorphic measurements

The height and the weight were measured in light underclothing without shoes The height was recorded with an accuracy of 0 5 cm the weight with an accuracy of 0 5 kg

The height and weight readings yielded the value of overweight when the weight (W) was divided by the height (H)

$\frac{W}{H}$ weight/height index (Khosla and Lowe 1967)

Although this index is not the best of the indexes constructed on the basis of the height and weight it is simple and was therefore considered suitable for this investigation particularly as obesity was also verified by skinfold measurements The triceps and the sub scapular skinfolds were measured according to standardized instructions (Rose and Blackburn 1968) The results were recorded with an accuracy of 1 mm



20°
30°
70°
ARCTIC
CIRCLE
Oulu
Haapavesi
Turku
Helsinki
60°

version of the Minnesota Code (Rose and Blackburn 1968) was used

The subjects examined were divided into two groups on the basis of the ECG

1 ECG-positive (pathological ECG)

2 ECG-negative

The subjects in whom one or several of the following changes were noted were ECG-positive

I Minnesota code 1 1 ("major Q)

II Minnesota code 4 1 5 1 5 2 ("major ST/T depression)

III Minnesota code 6 1 (complete A V block) 7 1 (complete left bundle branch block) and 8 3 (atrial fibrillation)

The others were ECG-negative

Minnesota codes used as criteria of pathological ECG

1 1 1 Q/R amplitude ratio 1/3 or more plus Q duration 0 03 sec or more in any of leads I II V2 3 4 5 6

1 1 2 Q duration 0 04 sec or more in any of leads I II V1 2 3 4 5 6

1 1 3 Q duration 0 04 sec or more plus R amplitude of 3 mm or more in lead aVL

1 1 4 Q duration 0 05 sec or more in lead III plus any Q wave of at least 1 0 mm amplitude in aVF

1 1 5 Q duration 0 05 sec or more in lead aVF

1 1 6 QS patterns when R wave is present in adjacent lead to the right on the chest in any of leads V2 3 4 5 6

Blood pressure

The blood pressure was recorded from the right upper extremity in a sitting position according to the WHO *instructions (Rose and Blackburn 1968)* Diastolic pressures were taken at the fifth phase (i e point of disappearing of all sounds) A mercury manometer with a *12 x 25 cm cuff was used* The reading was taken with an accuracy of 5 mmHg

The blood pressures were recorded by three local public health nurses on alternate days Blood pressure measurements are part of their daily routine which has given them a fairly wide experience Despite this the manner of recording the blood pressure was controlled for each of the three nurses before starting the examinations so that *the technique of measurement would be as identical as possible in all* cases

Electrocardiograms

The apparatus employed was Hewlett Packard s *ECG-phonosystem 1514 A* which meets the criteria set for ECG equipment (American Heart Association 1967 Krikler and Macfarlane 1974) Paper speed was 50 mm/s and calibration 1 mV/cm ECG was recorded 1 5 2 hours after the glucose administration according to the WHO instructions (Rose and Blackburn 1968) The leads I II III aVR aVL aVF V1 V6 were used All the ECG recordings and interpretations were made by the author

Pathological ECG

There are several ECG classifications now available which are suited to mass surveys (Blackburn et al 1960 Astrand et al 1967 Punsar et al 1968 Blackburn 1969) *In interpreting the present ECGs* the WHO

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1 1 3 Q duration 0 04 sec or more plus R amplitude of 3 mm or more in lead aVL

1 1-4 Q duration 0 05 sec or more in lead III plus any Q wave of at least 1 0 mm amplitude in aVF

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1-1-7 QS pattern in all of leads V1-V4 V1-V5 or V1-V6

4 1 S T-J depression 1 0 mm or more and S-T segment horizontal or downward sloping in any of leads I II aVL aVF V2 3 4 5 6 (requires a T-wave code in 5)

5-1 T amplitude negative minus 5 mm or more in any of leads I II V2 3, 4 5 6 or in lead aVL when R amplitude is 5 mm or more or in lead aVF when QRS is mainly upright

5-2 T amplitude negative or diphasic (positive-negative or negative--positive type) with negative phase at least minus 1 0 mm but not as deep as minus 5 mm in any of leads I II V2 3 4 5 6 or in lead aVL when R amplitude is 5 mm or more or in lead aVF when QRS is mainly upright

6 1 Complete (third degree) A V block (permanent of intermittent) in any lead

7-1 Complete left bundle branch block

8-3 Atrial fibrillation

Comparison of risk factors and pathological ECG

The correlation of the following factors to pathological ECG was investigated cholesterol triglycerides systolic and diastolic blood pressure declined glucose tolerance overweight and obesity as well as smoking and occupation

The comparison was accomplished by dividing the subjects into five equally large groups (quintiles) on the basis of each risk factor and finding out the proportion of ECG-positive subjects in each quintile The comparison for smoking and occupation was carried out differently

If we take cholesterol as an example quintile 1 consisted of indi viduals having the lowest 20 % of the values quintile 2 comprised the following 20 % etc Quintile 5 thus represents the subjects with the highest cholesterol values

The same procedure was used for the other risk factors the glucose quintiles were based on the 2-hour glucose value and all those with veri fied manitest diabetes who could not take the 2-hour glucose tolerance test were placed in quintile 5 The overweight quintiles were constructed on the basis of the weight/height index the subjects in quintile 1 had the lowest indexes those in quintile 5 the highest For the obesity quintiles the sum of the triceps and subscapular skinfolds was used with the individuals in quintile 1 having the smallest folds and those in quintile 5 the largest

Smoking and pathological ECG

The subjects were divided into three main groups on the basis of smoking smokers (1) ex smokers (2) and non-smokers (3) (Rose & Black burn 1968) The proportions of pathological ECG values were compared in the different age-groups and the two sexes

The smokers were further divided into sub-groups on the basis of the quantity and quality of the tobacco consumed and the proportions of ECG-positive and ECG-negative subjects in the two sexes were compared in these sub-groups

Occupation and pathological ECG

The population examined was divided into the following occupational groups

1 = heavy manual work (farmer farmer s wife heavy household work with cattle raising lumbering)

2 = supervision stress job (teacher salesman shopkeeper physician)

3 = office work or light sedentary work (office clerk car transport service)

4 = standing work (shop assistant waiter/waitress nurse)

5 = household work (no cows)

6 = disabled pensioner

These occupational groups have been constructed on the basis of the classification proposed by Rauhala (1966) and an attempt has been made to adjust them to the local conditions

The proportions of pathological ECG values in the different age groups of the occupational categories were recorded for both sexes

Statistical methods

The t test (Woolf 1968 a) and a modified t-test (Woolf 1968 b) were used in comparing the means and the different ratios

The degree of significance were as follows

Almost significant (the propability was less than 5 % or $p < 0\ 05$)

Significant (less than 1 % or $p < 0\ 01$)

Highly significant (less than 0 1 % or $p < 0\ 001$)

Tree analysis

The correlations between the different risk factors and pathological ECG were examined with the help of the tree analysis or the AID (auto matic interaction detector) method (Sonquist et al 1974)

The method is applicable when there is one dependent variable and at least one independent variable The dependent variable must be

dichotomous or adaptable to an interval scale while the independent variable can be expressed with a nominal scale Each independent variable comprises two or more classes

The purpose of the method is to find the best combinations of independent variables making the differences between the observational items grouped on the basis of the combinations and the means of the dependent variable as great as possible The method resembles the stepwise regression analysis in that it advances step by step starting from the independent variables which are most clearly dependent on the dependent variable At each stage one group of observational items is divided into two The process is continued until no group can be divided on the basis of the criteria any longer The aim is to find the independent variables which correlate best with the dependent variable and their optimal combinations The essential findings are expressed with a figure where the stepwise formation of the groups the cutting points employed the group means in the dependent variable and the size of the final groups are presented The ultimate result yielded by this method is hence largely qualitative

At the first stage all the items are dealt with as one group The division into two groups is made by the independent variable and at the point which makes the sum of squares between the groups in the dependent variable as great as possible In the group I which is to be divided the best point of intersection for each explaining variable is sought as follows

Let TSS be the total variance of the variable to be explained in the material and TSSI the corresponding total variance in the group I to be divided (if $TSSI/TSS \leq P1$ no attempt is made to divide group I) and let BSS be the variance between the two groups obtained by dividing

1 = heavy manual work (farmer farmer s wife heavy household work with cattle raising lumbering)

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The method is applicable when there is one dependent variable and at least one independent variable The dependent variable must be

MAXGP the greatest permitted number of final groups The criterion ensures that no more groups are obtained than has been considered ex pedient for the investigation in advance

RMIN the smallest permitted number of observational items in the group If a group has fewer items than 2RMIN it is no longer divided because at least one of the resulting groups would have fewer items than RMIN This criterion prevents the differentiation of a few highly deviating items into a group of their own

The condition of each criterion must be realized before the group can be divided When the condition of MAXGP is fulfilled the process is terminated while the other conditions pertain to single groups

It must further be made clear whether the independent variables are expressed with a nominal scale or an ordinal or some more complex scale On the basis of this information the program treats the variables in different ways The classes of a variable expressed with a nominal scale are set in an order on the basis of their means in the dependent vari able but the order of the classes of the variables expressed with an ordinal or some other scale is retained While searching for the cutting point the program then divides the observational items into two groups at each class boundary examining whether the criteria are realized and tabulating the result It further tabulates the best cutting point for each variable According to the P2 criterion the best cutting points of the different variables are then examined for the point which is used to divide the group into two

The final groups obtained as the result of the analysis can be dif ferent small groups explained groups and unexplained groups The group is small whenever the number of items is too small for the RMIN criterion to allow further division The group is explained when it is so homogenous that the P1 criterion shows the variance to be so small as to allow no further division The group is unexplained if it contains

group I The ratio BSS/TSSI is calculated for each informative variable at each point of intersection The greatest of these ratios corresponds to the best division which can be made by the variable to be explained The variable represented by the greatest ratio BSS/TSSI is chosen as the basis of the division The division is made if the ratio BSS/TSS thereby obtained $\geq$ P2 It is further checked that the criteria MAXGP and RMIN are valid

This procedure guarantees the minimum variance of the dependent variable so far unexplained When the entire material has been divided into two groups like this the group with the greatest total sum of squares in the dependent variable is chosen to be examined next In other words the group as unhomogeneous as possible from the viewpoint of the dependent variable is chosen to be considered first because the variance within it is great and it can most likely be further divided into groups The division of this group yields again two groups which gives us a total of three groups The group with the greatest total sum of squares in the dependent variable is chosen to be considered next The process is then continued in the same way until none of the groups can be divided any longer according to the guiding criteria

The formation of groups is guided by four criteria

P1 = the proportion of the total sum of squares of the dependent variable which represents the minimum internal variance of the group required for the group to be divided The variation range of the criterion is 0 00001 $\leq$ P1 $\leq$ 1 0 This criterion prevents the division of very homogenous groups

P2 = the proportion of the total sum of squares of the dependent variable which represents the minimum sum of squares between the groups obtained in the best division The variation range of the criterion is 0 $\leq$ P2 $\leq$

MAXGP the greatest permitted number of final groups The criterion ensures that no more groups are obtained than has been considered ex pedient for the investigation in advance

RMIN the smallest permitted number of observational items in the group If a group has fewer items than 2RMIN it is no longer divided because at least one of the resulting groups would have fewer items than RMIN This criterion prevents the differentiation of a few highly deviating items into a group of their own

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variance but no independent variable can be used to divide it into two in such a way that a proportion of the variance required by the P2 cri terion would be explained

RESULTS

Prevalence of pathological ECG

The total series included 319 ECG-positive subjects who account for 20 5 % 28 of them or 8 7 % of all the ECG-positive subjects be longed to group I ("major Q) 238 or 88 8 % to group II ("major ST/T depression) and 8 or 2 5 % to group III (complete A V block 1 complete left bundle branch block 5 and atrial fibrillation 2) Tables 1 and 2

There were 210 ECG-positive women who accounted for 26 5 % of the total female series (793) 6 of them or 0 8 % belonged to group I 202 or 25 5 % to group II and 2 or 0 3 % to group III Table 1

The ECG-positive men numbered 109 accounting for 14 3 % of the total male series (761) 22 or 2 9 % belonged to group I 81 or 10 6 % to group II and 6 or 0 8 % to group III

Pathological ECG in the different age groups. Tables 1 and 2, figure 1

In women the proportion of pathological ECG values increases evenly along with age there is a clear difference between the youngest and the oldest age group ($p < 0\ 001$)

In men the proportion of ECG-positive findings first increases clearly the difference between the youngest and the next oldest group is signifi cant ($p < 0\ 01$) but from 45 years onwards the prevalence of positive ECG findings remains unchanged

A comparison of men and women shows that women have more ECG changes than men in the total series ($p < 0\ 001$) In each age group too more women have pathological ECG than men in the youngest and oldest age groups the difference is highly significant ($p < 0\ 001$) Pathological Q changes on the other hand are considerably more frequent among men than women ($p < 0\ 001$)

Table 1 ECG finding specified Women by age groups

I = major Q (Minn 1 1)

II = major ST/T depression (Minn 4 1 5 1 5 2)

III = others (Minn 6 1 7 1 8 3)

Age group	I	II	III	Total
40 - 44 233 subjects	0 = 0 %	42 = 18 0 %	0 = 0 %	42 = 18 0 %
45 - 49 197	0 = 0 %	46 = 23 4 %	1 = 0 5 %	47 = 23 9 %
50 54 197	1 = 0 5 %	55 = 27 9 %	0 = 0 %	56 = 28 4 %
55 59 166	5 = 3 0 %	59 = 35 5 %	1 = 0 6 %	65 = 39 1 %
Total 793	6 = 0 8 %	202 = 25 5 %	2 = 0 3 %	210 = 26 5 %

Table 2 ECG finding specified Men by age groups I II and III as in table I

Age group	I		II		III		Total	
40 44 229 subjects	3	1 3 %	13	5 7 %	1 =	0 4 %	17	7 4 %
45 49 202	5	2 5 %	25	12 4 %	2	1 0 %	32	15 9 %
50 54 161	6	3 7 %	22	13 7 %	1 =	0 6 %	29	18 0 %
55 59 169	8	4 7 %	21	12 4 %	2	1 2 %	31	18 3 %
Total 761	22	2 9 %	81	10 6 %	6	0 8 %	109	14 3 %

Figure 1 Pathological ECG in the different age groups

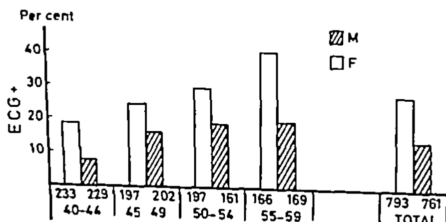


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55 59 166	5 = 3 0 %	59 = 35 5 %	1 = 0 6 %	65 = 39 1 %
Total 793	6 = 0 8 %	202 = 25 5 %	2 = 0 3 %	210 26 5 %

Summary

No correlation appears between cholesterol and pathological ECG

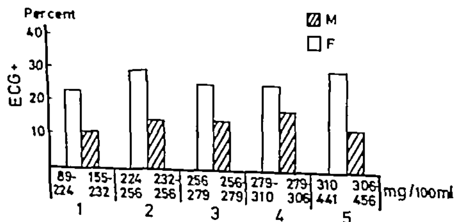
Table 3 Cholesterol means (mg/100 ml) in the different age groups

Age group	Women	SD	Men	SD
40 44	260	44 6	267	47 6
45 49	262	46 5	270	47 2
50 54	276	51 1	270	46 5
55 59	275	54 0	279	44 2
Total	268	49 3	271	46 5

Table 4 Cholesterol means (mg/100 ml) and pathological ECG

		SD
ECG-positive women	271	52 0
ECG-negative women	266	48 4
ECG-positive men	274	41 0
ECG-negative men	270	47 6

Figure 2 Cholesterol quintiles and pathological ECG



Serum cholesterol

The mean cholesterol in the entire series was 269 mg/100 ml The mean for women was 268 mg/100 ml and that for men 271 mg/100 ml the difference is not significant Table 3

The mean cholesterol value increased along with increasing age in both sex groups (women $p < 0\ 01$ men $p < 0\ 05$) Table 3

The mean cholesterol for the ECG-positive women was 271 mg/100 ml and the mean for the ECG-negative women 266 mg/100 ml The corres ponding values for men were 274 and 270 The differences were not significant in either sex group Table 4

The ECG-positive women who had a pathological Q wave (6) had a mean cholesterol values of 268 mg/100 ml It does not differ from the mean cholesterol value of the ECG negative women (266 mg/100 ml)

Correspondingly the men with a pathological Q wave (22) had the same mean cholesterol value as all the ECG positive men i e 274 mg/ 100 ml When this is compared with the cholesterol mean of the ECG-- negative men (270 mg/100 ml) no significant difference can be seen

Cholesterol quintiles and pathological ECG Figure 2

When the series is divided into quintiles according to the cholest erol values and the proportion of ECG positive subjects is examined in each quintile it appears that both men and women show a minor differ ence between the lowest and the highest quintile but this difference is not significant

The three middle quintiles of men contained more ECG-positive sub jects than either the first or the last but no significant differences appeared between any groups ECG changes thus do not increase along with increasing cholesterol values in either sex though the variation of cholesterol values is 89 441 mg/100 ml in women and 155 456 mg/ 100 ml in men

Summary

In the female series there is no correlation between triglycerides and pathological ECG

In the male series there is some correlation the men with a pathological Q wave in their ECG had higher serum triglyceride levels on an average than the ECG-negative men

Table 5 Triglyceride means (mmol/l) in the different age groups

Age group		Women	SD	Men	SD
40	44	1 1	0 5	1 3	0 7
45	49	1 2	0 8	1 3	1 0
50	54	1 3	0 6	1 3	0 7
55	59	1 3	0 6	1 4	1 0
Total		1 2	0 6	1 3	0 8

Table 6 Triglyceride means (mmol/l) and pathological ECG

		SD
ECG-positive women	1 2	0 6
ECG-negative women	1 2	0 7
ECG-positive men	1 4	1 0
ECG negative men	1 3	0 8

Serum triglycerides

The mean triglyceride value in the whole series was 1 25 mmol/l The value for women was 1 2 mmol/l and that for men 1 3 mmol/l the difference being almost significant ($p <$ 0 05) Table 5

In women the value for triglycerides clearly increased along with age ($p <$ 0 001) while in men age was not significantly related to serum triglycerides Table 5

Both ECG-positive and ECG-negative women had a mean triglyceride value of 1 2 mmol/l The corresponding values in the male series were 1 4 and 1 3 which values did not differ significantly Table 6

The 6 ECG-positive women with a pathological Q wave had a tri glyceride mean of 1 1 mmol which does not differ from the corres ponding value of the ECG-negative women (1 2 mmol/l) The men with a pathological Q wave on the other hand had a clearly higher tri glyceride mean (1 7) than the ECG-negative men (1 3) ($p <$ 0 001)

Triglyceride quintiles and pathological ECG Figure 3

When the series is divided into quintiles according to the triglyc eride values and the proportion of ECG positive subjects in each quin tile is examined it can be seen that there are no significant differ ences between the groups of either sex although the triglyceride val ues in at least the first and the last quintile are considerably dif ferent

The proportion of ECG-positive men is smaller in the first quintile than in the others but this difference is not statistically signifi cant either

ECG changes thus do not increase along with increasing triglyceride values in either sex although the variation of triglyceride values is 0 2 - 9 5 mmol/l in women and 0 2 - 9 3 mmol/l in men

Summary

In the female series there is no correlation between triglycerides and pathological ECG

In the male series there is some correlation the men with a pathological Q wave in their ECG had higher serum triglyceride levels on an average than the ECG-negative men

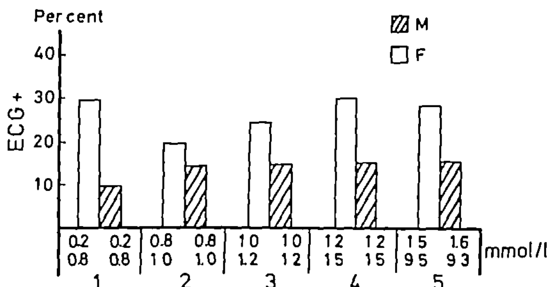
Table 5 Triglyceride means (mmol/l) in the different age groups

Age group	Women	SD	Men	SD
40 44	1 1	0 5	1 3	0 7
45 49	1 2	0 8	1 3	1 0
50 54	1 3	0 6	1 3	0 7
55 59	1 3	0 6	1 4	1 0
Total	1 2	0 6	1 3	0 8

Table 6 Triglyceride means (mmol/l) and pathological ECG

		SD
ECG-positive women	1 2	0 6
ECG-negative women	1 2	0 7
ECG-positive men	1 4	1 0
ECG-negative men	1 3	0 8

Figure 3 Triglyceride quintiles and pathological ECG



Systolic and diastolic hypertension

The mean blood pressure in the total series was 157/94 being 161/94 in the female group and 152/93 in the male group The diastolic values do not differ from each other but women have clearly higher systolic blood pressure than men ($p < 0\ 001$) Table 7

In women both systolic and diastolic blood pressure increase along with age up until the age of 50 ($p < 0\ 001$) In men systolic blood pressure increases evenly along with age ($p < 0\ 01$) while diastolic blood pressure remains unchanged Table 7

The ECG-positive women have distinctly higher systolic and diastolic blood pressure than the ECG negative women ($p < 0\ 001$) A corresponding difference ($p < 0\ 001$) can also be seen in the systolic pressure of the ECG positive men but the difference in diastolic pressure is not equally clear ($p < 0\ 05$) Table 8

The women with a pathological Q wave in their ECG had a mean blood pressure of 160/94 which is not clearly different from the mean of the ECG-negative women The men with a Q wave had a mean blood pressure of 157/94 the systolic pressure being clearly higher than the value for ECG-negative men ($p < 0.01$) The male groups did not differ as regards diastolic blood pressure

Blood pressure quintiles and pathological ECG - Figures 4 and 5

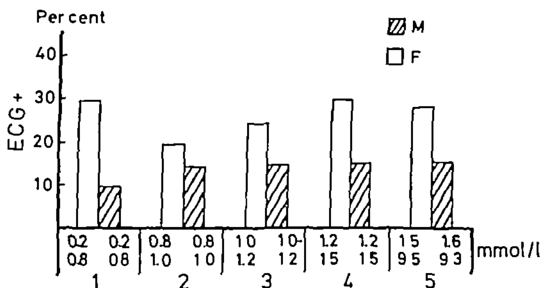
The quintiles of systolic blood pressure (figure 4) show that the proportion of pathological ECG values increases along with increasing systolic blood pressure in the female series the difference between the first and the last quintile is almost significant ($p < 0.05$) No similar trend can be seen in the male series only the last quintile contains more ECG-positive subjects than the other ones but the differences between the first and the last quintile is not statistically significant

The relationship between diastolic blood pressure and pathological ECG (figure 5) in the female group appears similar to the relationship between systolic pressure and pathological ECG positive ECGs increase along with increasing diastolic pressure Yet there is no significant difference between the first and the last quintile In the male series diastolic blood pressure behaves similarly to systolic pressure only the last quintile differs clearly from the others but the difference is not statistically significant

Summary

In women both the systolic blood pressure and the diastolic pressure increase up until the age of 50 and both of the pressures are higher in

Figure 3 Triglyceride quintiles and pathological ECG



Systolic and diastolic hypertension

The mean blood pressure in the total series was 157/94 being 161/94 in the female group and 152/93 in the male group The diastolic values do not differ from each other but women have clearly higher systolic blood pressure than men ($p < 0\ 001$) Table 7

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Figure 4 Systolic blood pressure quintiles and pathological ECG

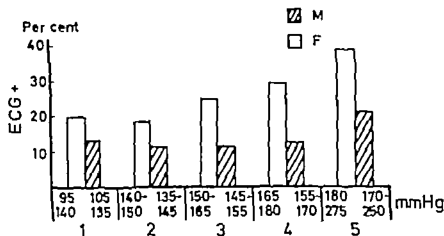
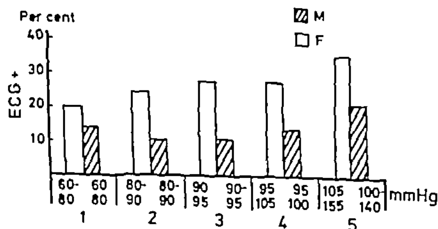


Figure 5 Diastolic blood pressure quintiles and pathological ECG



the ECG-positive subjects The ECG positive men had only the systolic pressure higher than the ECG negative men Q pathology is only associated with elevated systolic blood pressure in men

Table 7 Blood pressure means (mmHg) in the different age groups

Age group	Women	SD	Men	SD
40 - 44	150/90	21/11	148/93	21/13
45 - 49	156/93	25/13	151/93	23/13
50 - 54	171/98	30/15	154/93	23/13
55 - 59	173/97	30/14	156/94	23/12
Total	161/94	28/14	152/93	23/13

Table 8 Blood pressure means and pathological ECG

		SD
ECG positive women	168/97	31/14
ECG-negative women	158/93	26/13
ECG-positive men	159/95	27/15
ECG-negative men	151/93	22/13

The women who had a pathological Q wave in their ECG and who have possibly suffered a myocardial infarction had a higher mean 2 hour glucose tolerance value than the ECG-negative women

Table 9 2 hour blood sugar means (mg/100 ml) in the different age groups

Age group	Women	SD	Men	SD
40 44	110 3	36 0	101 2	29 7
45 49	109 7	33 9	109 4	34 9
50 54	123 1	42 1	108 2	36 6
55 59	124 4	49 7	115 4	38 6
Total	116 2	40 7	108 0	35 0

Table 10 2 hour blood sugar means (mg/100 ml) and pathological ECG

		SD
ECG-positive women	119 8	40 1
ECG-negative women	114 9	40 8
ECG-positive men	109 6	34 9
ECG-negative men	107 7	34 9

Diabetes mellitus and glucose intolerance

The 2-hour mean for blood glucose was 112 1 mg/100 ml in the whole series being 116 2 in the female group and 108 0 mg/100 ml in the male group The difference between the means of men and women is unambiguous ($p < 0$ 001) Table 9

The 2-hour mean for blood glucose increases along with age in both women ($p < 0$ 01) and men ($p < 0$ 001) Table 9

The mean 2 hour blood glucose of the ECG-positive women was 119 8 mg/100 ml and that of the ECG-negative women 114 9 mg/100 ml These values are not significantly different The corresponding values of men did not differ significantly either Table 10

The ECG-positive women with a pathologic Q wave had a mean 2 hour blood glucose value of 149 2 mg/100 ml which is clearly higher than the corresponding mean of the ECG-negative women ($p < 0$ 001) No parallel difference was noted in the male series

Glucose quintiles and pathological ECG Figure 6

When the series is divided into quintiles on the basis of the 2 hour blood glucose values it can be seen that the proportions of ECG positive subjects are the same in all quintiles of both men and women no statistically significant differences can be seen

Even though quintile 5 represents subjects with clearly diabetic metabolism not even this quintile included more ECG positive subjects than the others

Summary

Depressed glucose tolerance and pathological ECG were not found to correlate in either sex group according to the quintile method

the other ones is not significant Figure 8

In the male series the skinfold sums yield the same result as the overweight quintiles the last quintile contains fewer ECG-positive subjects than the first The differences are not significant Figure 8

An examination of the means of ECG-positive and ECG-negative subjects shows no differences in weight height or the thickness of skinfolds in either sex group Table 15

The tables 11 14 show the means for weight height and the thickness of skinfolds

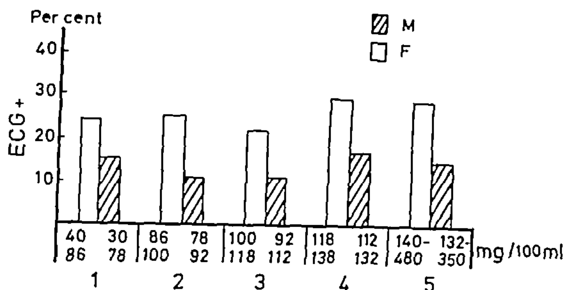
Summary

Pathological ECG thus does not clearly correlate with overweight or obesity in either sex although the women with marked overweight and obesity had somewhat more pathological ECG values

Table 11 Means

		Women	SD	Men	SD
Height	cm	156 5	5 5	168 5	6 2
Weight	kg	68 5	13 2	72 6	11 2
Triceps	mm	21 1	7 4	9 2	4 5
Subscap	mm	21 5	9 6	13 9	6 8

Figure 6 Depressed glucose tolerance and pathological ECG



Overweight and obesity

The first four of the quintiles constructed on the basis of the weight/height index (overweight) contain almost equal proportions of ECG-positive women only the last quintile includes more such subjects The difference between the last quintile and the others ones is not however statistically significant Figure 9

All the male quintiles include more or less equal proportions of ECG-positive subjects the last quintile has even fewer pathological ECG than the first The differences are not significant Figure 7

In the quintiles constructed on the basis of the skinfold sum (obesity) the proportion of ECG-positive women increases as the skin fold sum increases yet the difference between the last quintile and

Table 15 Comparison of the means of ECG-positive and ECG-negative subjects

		ECG+ women	ECG- women	ECG+ men	ECG- men
Height	cm	155 8	156 7	168 2	168 5
Weight	kg	68 3	68 6	73 9	72 3
Triceps	mm	21 2	21 1	9 9	9 1
Subscap	mm	21 2	21 5	14 6	13 7

Figure 7 Quintiles constructed from the weight/height index (over weight) and pathological ECG

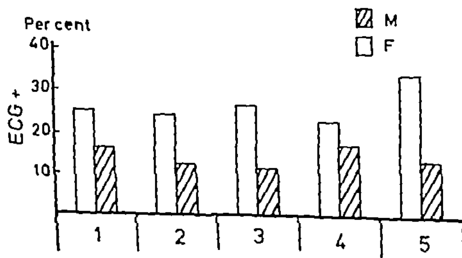


Table 12 Height means in the different age groups of women and men

	Women	SD	Men	SD
40 - 44	157 6	5 1	169 9	6 0
45 - 49	157 0	5 5	168 3	6 1
50 - 54	156 1	5 7	168 0	6 3
55 - 59	154 6	5 2	167 3	6 2

Table 13 Weight means in the different age groups of women and men

	Women	SD	Men	SD
40 44	67 1	13 2	73 7	11 3
45 - 49	67 9	11 9	72 9	10 9
50 54	70 9	14 1	72 8	11 2
55 - 59	68 6	13 3	70 6	11 3

Table 14 Skinfolds (triceps + subscapular) in the different age groups of women and men

	Women	SD	Men		SD
40 - 44	19 8 + 19 7 = 39 5	12 2	9 1 + 13 6	22 7	8 4
45 - 49	21 5 + 21 8 43 3	12 0	9 1 + 13 7	22 8	7 9
50 - 54	22 3 + 23 0 45 3	12 7	9 6 + 14 9	24 5	8 8
55 - 59	21 3 + 21 7 = 43 0	11 1	9 2 + 13 3	23 5	7 7

If we examine the division of the ECG-positive men into the dif ferent age groups we can see that the youngest age group (40 44 yr) has highly significantly fewer ECG changes ($p < 0.001$) in non smokers than in ex smokers or smokers The differences level off as we move into the older age groups where the smokers ex smokers and non-smok ers are not different except in the age group of 50 54 yr where ex smokers have more ($p < 0.01$) ECG changes than non-smokers

In the female series (table 17 figure 9) ECG changes were most numerous in the group of non-smokers and least numerous in the groups of smokers but no significant differences can be seen between the smoking groups

Women have the same proportion of ECG changes in all the smoking groups of the different age groups except in the age group of 50 54 yr where non-smokers have clearly more ($p < 0.001$) ECG findings than the others

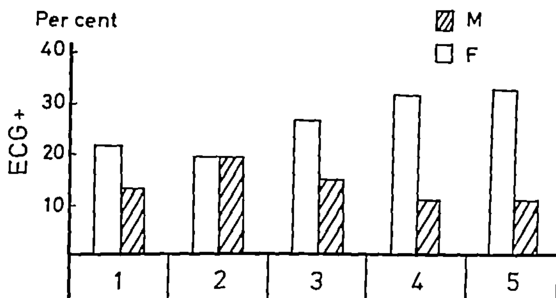
When the subjects are divided into groups on the basis of the amount of tobacco consumed (figures 11 and 12) it appears that there are equal proportions of ECG negative and ECG-positive subjects in all male and female groups This result has not been calculated for age groups but for the entire population investigated

Summary

Most of the women (78) were non-smokers while over half of the men (58 2 %) were smokers

In the female series smoking and pathological ECG did not correlate clea ly while i the youngest (40 44 yr) male group non-smokers had clearly ($p < 0.001$) fewer ECG findings than smokers and ex smokers The older male groups displayed no correlation between smoking and pathological ECG

Figure 8 Quintiles constructed from the skinfold sum (triceps + subscapular) (obesity) and pathological ECG



Smoking

More than half of the men were smokers (58 2 %) and an additional one quarter (24 9 %) had smoked previously Less than one fifth of the men were non smokers (17 9 %)

In the female series an opposite situation prevailed the majority (78 0 %) were non smokers and even ex-smokers were few in number 6 5 %

The smokers ex-smokers and non-smokers were divided evenly into the different age groups of both sexes Table 16

The ECG-positive men (table 17 figure 10) were fewest in the group of non smokers (10 4 %) and most numerous in the group of ex smokers (18 2 %) The corresponding percentage in the group of smokers was 13 3 % These percentages are not significantly different

If we examine the division of the ECG-positive men into the different age groups we can see that the youngest age group (40 44 yr) has highly significantly fewer ECG changes ($p < 0.001$) in non-smokers than in ex smokers or smokers The differences level off as we move into the older age groups where the smokers ex-smokers and non-smokers are not different except in the age group of 50 54 yr where ex smokers have more ($p < 0.01$) ECG changes than non-smokers

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When the subjects are divided into groups on the basis of the amount of tobacco consumed (figures 11 and 12) it appears that there are equal proportions of ECG-negative and ECG-positive subjects in all male and female groups This result has not been calculated for age groups but for the entire population investigated

Summary

Most of the women (78 %) were non-smokers while over half of the men (58 2 %) were smokers

In the female series smoking and pathological ECG did not correlate clearly while in the youngest (40 44 yr) male group non-smokers had clearly ($p < 0.001$) fewer ECG findings than smokers and ex smokers The older male groups displayed no correlation between smoking and pathological ECG

Table 16 The different smoking groups

Age group	Smokers		Ex-smokers		Non smokers	
	F	M	F	M	F	M
40 - 44	24	129	16	42	187	53
	10 6 %	57 6 %	7 1 %	18 7 %	82 3 %	23 7 %
45 - 49	34	119	12	49	148	32
	17 5 %	59 5 %	6 2 %	24 5 %	76 3 %	16 0 %
50 - 54	27	97	12	41	154	26
	14 0 %	59 2 %	6 2 %	25 0 %	79 8 %	15 8 %
55 59	20	92	10	55	131	23
	12 4 %	54 1 %	6 2 %	32 4 %	81 4 %	13 5 %
Total	105	437	50	187	620	134
	13 5 %	58 2 %	6 5 %	24 9 %	78 0 %	17 9 %

Table 17 Pathological ECG in the different smoking groups

Age group	Smokers F	Smokers M	Ex smokers F	Ex smokers M	Non-smokers F	Non-smokers M
40 44	4	12	3	4	34	1
	16 7 %	9 3 %	18 8 %	9 5 %	18 2 %	1 9 %
45 49	6	19	4	8	35	6
	17 7 %	16 0 %	33 3 %	16 3 %	23 7 %	18 8 %
50 54	4	14	1	10	51	3
	14 8 %	14 4 %	8 3 %	24 4 %	38 9 %	11 5 %
55 59	8	13	3	12	51	4
	40 0 %	14 1 %	30 0 %	21 8 %	38 9 %	17 4 %
Total	22	58	11	34	171	14
	21 0 %	13 3 %	22 0 %	18 2 %	27 6 %	10 4 %

Fig 9 Pathological ECG in the different smoking groups Women

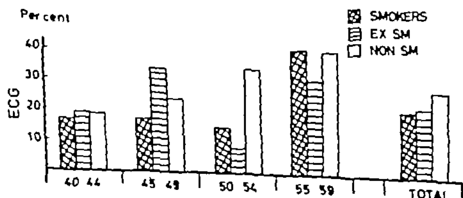


Figure 10 Pathological ECG in the different smoking groups Men

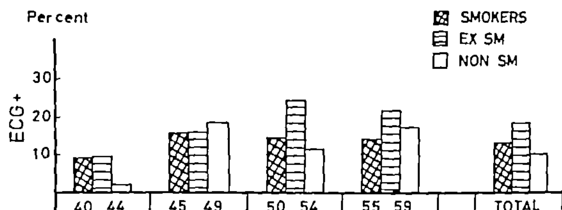


Figure 11 ECG-positive and ECG-negative subjects in the different smoking groups Women

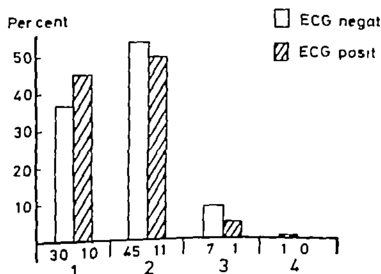
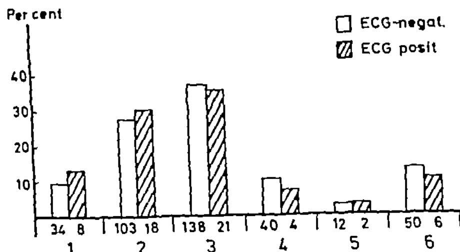


Figure 12 ECG-positive and ECG-negative subjects in the different smoking groups Men



Occupation

More than half of both men and women were engaged in heavy manual work (men 66 4 % women 56 2 %) The second biggest male group consisted of men on disability pension who accounted for as many as 16 5 % of all men The second biggest female group (21 2 %) consisted of women doing household work (without cattle) The proportions of all the other occupational groups of both men and women were quite evenly under 10 % Tables 18 and 19 figure 13

The men in the first four occupational groups have fairly equal proportions of ECG changes The ECG changes were most numerous in the group of pensioners (29 6 %) and next numerous in the group of men doing household work but the small number of subjects in the

Figure 10 Pathological ECG in the different smoking groups Men

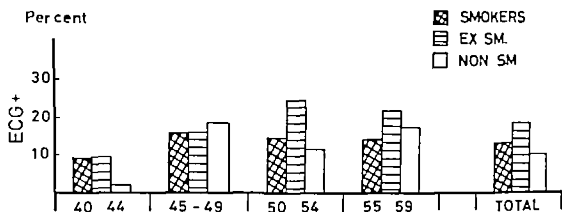


Figure 11 ECG-positive and ECG-negative subjects in the different smoking groups Women

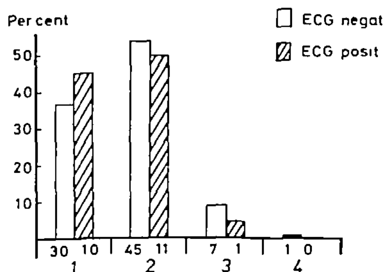
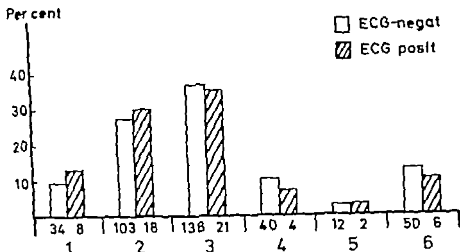


Figure 12 ECG-positive and ECG-negative subjects in the different smoking groups Men



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The men i the first four occupational groups have fairly equal proportions of ECG changes The ECG changes were most numerous in the group of pensioners (29 6 %) and next numerous in the group of men doing household work but the small number of subjects in the

latter group must be borne in mind Table 21 *figure* 17

In the female series the ECG changes were also most numerous in the group of pensioners (43 3 %) and next numerous in the group doing *household* work (33 8 %) The third group in frequency consisted of women doing heavy manual work of whom one fourth had pathological ECG findings (25 4 %) Group 2 (supervision teacher) included only one woman with pathological ECG out of a total of 23 women Table 20 and figure 14

Summary

The subjects on disability pension had clearly the most ECG changes particularly in the female series

In the other occupational groups men had equal proportions of ECG changes while the women doing household work any heavy manual work had the most changes

Occupational groups in the population investigated Figures 16 17 Tables 18, 19, 20, 21

1 = heavy manual work (farmer farmer s wife heavy household work with cattle lumbering)

2 supervision stress job (teacher salesman shopkeaper doctor etc)

3 = office work or corresponding (clerk car transport service etc)

4 = standing work (shop assistant waiter/waitress nurse etc)

5 household work (no cattle)

6 disabled pensioner hardly any work

Table 18 19 The occupational distribution of the population investigated

Women	Occupational groups					
Age group	1	2	3	4	5	6
40 44	147	11	12	19	32	10
45 49	116	9	14	15	38	6
50 54	104	0	5	13	52	18
55 59	74	3	6	4	44	33
Total	441	23	37	51	166	67
	56 2 %	2 9 %	4 7 %	6 5 %	21 2 %	8 5 %

Men	Occupational groups					
Age group	1	2	3	4	5	6
40 44	174	15	18	5	3	10
45 49	139	15	12	4	2	27
50 54	96	11	7	6	3	40
55 59	92	12	7	2	7	48
Total	501	53	44	17	15	125
	66 4 %	7 0 %	5 8 %	2 3 %	2 0 %	16 5 %

... in the diffe nt occ pational g oup Women

Age group	1		2		3		4		5		6	
	ECG +	ECG + %	ECG +	ECG + %	ECG +	ECG +	ECG +	ECG +	ECG +	ECG +	ECG	ECG
40 44	26	17 7	0	00 0	1	8 3	2	10 5	8	25 0	5	50 0
45 49	29	25 0	1	11 1	4	28 6	4	26 7	7	18 4	2	33 3
50 - 54	29	27 9	0	00 0	1	20 0	3	23 1	18	34 6	5	27 8
55 - 59	28	37 8	0	00 0	1	16 7	0	00 0	18	40 9	17	51 5
Total	112	25 4	1	4 4	7	18 9	9	17 6	51	33 8	29	43 4

Table 21 ECG-positive subjects in the different occupational groups Men

Age group	1		2		3		4		5		6	
	ECG +	ECG + %	ECG +	ECG + %	ECG +	ECG + %	ECG +	ECG + %	ECG +	ECG %	ECG +	ECG +
40 - 44	9	5 2	2	13 3	1	5 6	1	20 0	1	33 3	3	30 0
45 49	20	14 4	3	20 0	2	16 7	0	00 0	0	00 0	8	29 6
50 54	12	12 5	0	00 0	1	14 3	1	16 7	0	00 0	13	32 5
55 - 59	10	10 9	3	25 0	0	00 0	0	00 0	2	28 6	13	27 1

Figure 13 Occupational groups in the population investigated

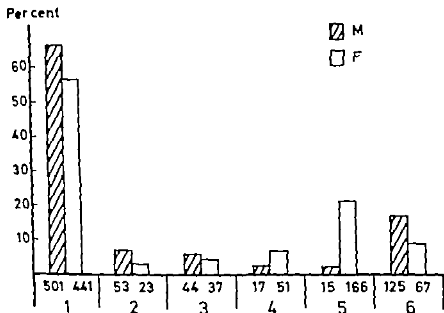
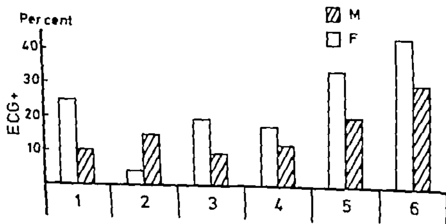


Figure 14 Pathological ECG in the different occupational groups



Correlations between the risk factors (Tree analyses)

Women

In the tree analysis of the female series the ECG variable correlated most strongly with systolic blood pressure exceeding 165 mmHg This correlation was later accompanied by age over 50 and occupation is such a way that pensioners and women doing heavy manual work and household work were included in the correlation Obesity was the final factor in this chain of correlations women who are thin and have normal skinfold thickness values have more ECG changes than obese women Figure 15

If we scrutinize the branch of lower systolic blood pressure in tree analysis we see that in addition to correlating with normal systolic blood pressure the ECG variable also correlates with occupation rendering pensioners and subjects with sedentary occupation the risk group The last item in this chain of correlations is pathological glucose tolerance

When the group of pensioners is excluded the ECG variable still correlates most strongly with systolic blood pressure It is worth noticing that when systolic blood pressure is low or normal (quintiles 1 2 3) no other correlating factors emerge Figure 16

The subjects with systolic blood pressure ≥ 165 mmHg (the 4th and 5th quintile) have age over 50 as the next correlating factor subjects younger than that have no additional risk factors A hypertonic woman aged over 50 next reflects the effect of occupation subjects with office work and standing work (shop assistant waitress etc) have many ECG changes Those doing heavy manual work and household work are clearly accompanied at the next stage by quintile 1 of the obesity

group which includes the thinnest women Quintile 5 of the obesity group for which the greatest skinfold thicknesses were recorded has already been left as a group of its own and clearly contains fewer ECG changes With regard to the occupational groups it can also be seen that group 2 (teacher shopkeeper etc) has not yet been included in the correlation

Triglycerides overweight and diastolic blood pressure appear only at the final end of the tree analysis

Summary

The tree analysis of the female series yielded the following results

1) Systolic blood pressure is the most important correlating factor being the only factor in women aged below 50 Low or normal systolic blood pressure did not correlate with any other factor in the analysis

2) Thin hypertonic women aged over 50 doing heavy manual work or household work constituted a risk group of their own Similarly hypertonic women over 50 doing office work or standing work (shop assistant waitress etc) also constitute a risk group without correlating obesity quintiles

3) Cholesterol and smoking were absent at all stages of the analysis

4) Triglycerides overweight and diastolic blood pressure appeared highly insignificant and depressed glucose tolerance entered the correlation only when it pertained to women on pension

Men

When we examine the mutual correlation of the different risk fac

tors to pathological ECG by means of the tree analysis (figure 17) we see that the strongest correlating factor is occupation This is due to the large group of pensioners (16 5 % of men were on pension) where ECG changes were numerous In the group of pensioners the ECG variable next correlated with smoking and the groups of ex and non smokers then correlated with triglycerides and age No unambiguous result was obtained for glucose tolerance In smoking pensioners the ECG changes correlated with high triglyceride values and high diastolic blood pressure

The other occupational groups displayed a clear correlation obesity (the two topmost quintiles) high systolic blood pressure (highest quintile) and high cholesterol (highest quintile) in this order The subjects belonging to the four lowest cholesterol quintiles had the following correlation age heavy or stationary work and high triglycerides

Since it seemed expedient to examine the correlations in the group of subjects still in active work the group of pensioners was excluded from the analysis and another tree analysis was obtained (figure 18) An unambiguous result was obtained a man who is thin or normal on the basis of his skinfolds and who does either heavy or stationary work is most strongly correlated with the ECG variable No other factors affect this correlation

Another unmistakable correlation was also established an obese man with exceedingly systolic blood pressure (highest quintile) and exceedingly high cholesterol (highest quintile) According to the present analysis cholesterol is significant only in combination with high systolic blood pressure and obesity

The obese men who were in the four lowest systolic blood pressure quintiles had overweight and triglycerides as the next correlating factors It is worth pointing out that high cholesterol was not included

in this chain the 46 men in the last branch of this chain had no pathological ECG changes

Summary

The tree analysis of the male series yielded the following result Two separate unambiguous risk groups emerged

1) a man who is thin or normal on the basis of his skinfold and who does heavy or stationary work (e g taxi driver)

2) an obese man with high systolic blood pressure and high cholesterol Cholesterol did not emerge as an independent risk factor

The following additional observations were made
smoking was present only a feature of the group of pensioners not of the other groups
the roles of triglycerides overweight diastolic blood pressure and age also remained fairly insignificant
depressed glucose tolerance did not emerge as a risk factor at any stage of the analysis

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Figure 16 Tree analysis in the female series after exclusion of the pensioners

IHD

718
(1)
2507
SYST B P
463 (2) 1,2,3 — 1987
255 (3) 4 5 — .3451
AGE
155 (5) 3 4 — 4322
100 (4) 1 2 — 2100
OCCUPATION
142 (6) 1 5 — 4648
13 (7) 3 4 — 7692
SUGAR
7 (8) 0 — 8571
135 (9) 1 2 3 4 5 — 4444
OBESITY
98 (10) 3 4 — 5102
37 (11) 5 — .2703
OBESITY
14 (12) 1 — 7142
84 (13) 2 3 4 — 4762
TRIGLY
29 (14) 1,2 — .3449
55 (15) 3 4 5 — .5455
OBESITY
21 (23) 3 4 — 4762
8 (22) 2 — .0000
OVERWEIGHT
8 (16) 1 2 — .8750
47 (17) 3 4 5 — 4894
DIAST BP
6 (26) 1 2 3 — 8333
15 (27) 4 5 — 3333
OVERWEIGHT
36 (19) 4 5 — .5833
11 (18) 3 — .1818
DIAST BP
11 (21) 5 — .8182
25 (20) 1,2 3 4 — 4800
SYST BP
15 (24) — 6667
10 (25) — 2000

Figure 15 Tree analysis in the female series

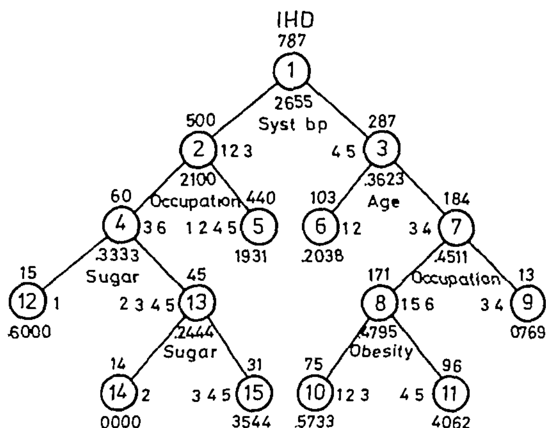
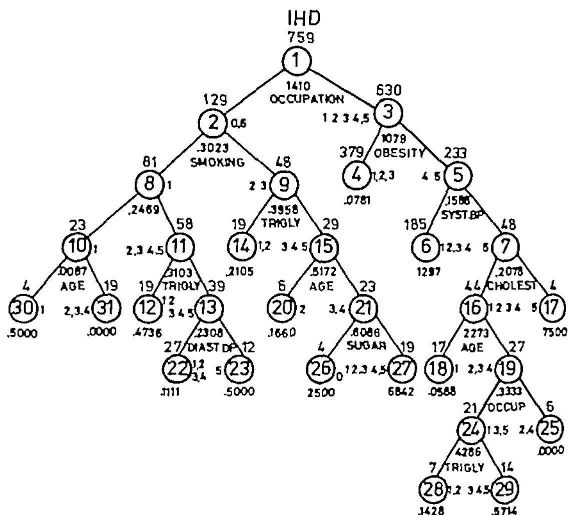


Figure 18 Tree analysis in the male series after exclusion of the pensioners

Figure 17 Tree analysis in the male series



The methods applied to the different mass surveys vary This variation also has some effect on the results making it difficult to compare the results of different mass surveys In order to reach the best level of standardization the WHO recommendations (Rose & Blackburn 1968) were observed in the present work but even so many of the methods remain open to discussion

Glucose tolerance test ECG

Glukodyn[R] glucose solution was used in the oral glucose tolerance test which solution turned out to be well tolerated by the subjects For practical reasons only one blood sample is taken either 1 hr or 2 hr after the administration of oral glucose in mass surveys Since the 2 hour glucose tolerance test is considered better (Stewart and Robertson 1963 Jackson et al 1968) it was used in this series of examinations In any case the 2 hour glucose tolerance test was well suited to the present project

In several mass screening surveys ECG has been recorded before the intake of glucose solution directly after the fact (e g Pybrälä et al 1973) In some other investigations however ECG recording has been performed after the administration of glucose solution (e g Welborn et al 1969) The WHO instruction states Whenever possible meals and glucose administration should precede the ECG recording by two hours (Rose G A & Blackburn H Cardiovascular Survey Methods World Health Organization monograph series n o 56 Geneva 1968 page 101) The ECG recording in this investigation was therefore performed 1 5 2 hr after the administration of glucose solution for practical reasons the recording could not be done after exactly 2 hours but had to be done a little earlier Immediately after recording the ECG the blood sample for the 2 hour glucose tolerance test was taken from each subject

DISCUSSION

General

Several methods can be used to verify IHD Autopsy reveals sclerosis of the coronary arteries and after a certain period has elapsed since the acute phase a myocardial infarction suffered by the patient Coronary angiography also shows the state of the coronary arteries but is inapplicable to mass surveys Anamnestic angina pectoris is a subjective criterion which does not necessarily indicate the presence of ischemic heart disease Electrocardiography is probably the most widely spread method for verifying IHD although it is not absolutely reliable either In the present work however ECG alone was used to verify IHD because it is the method with most documentary evidence for this use Only severe ECG changes were accepted as signs of IHD

Among the different mass screening surveys follow up investigations yield the best information on IHD and the factors correlating with it A cross-section study reveals only the contemporary situation giving much more restricted information than a follow-up study Cross sectional studies are generally accomplished within a short period and they may reveal factors which turn out as important risk factors of IHD in a longitudinal study Still cross sectional studies always have certain limitations compared with longitudinal studies for example if a heavy smoker dies a sudden death he is not included in the cross sectional study Conversely however the different cross sectional findings may reflect the various risk factors of IHD in different population Taking into account the small number of the reports on IHD and risk factors in women it was considered useful to present the results of this cross section study The intention is to continue this work as a follow up investigation

mass screening ECG is the only standardized objective method which fulfils the condition It is known on the other hand that the ECG changes brought about by coronary disease are not fully specific to the disease and that coronary disease does not always entail ECG changes which means that sensitivity is also restricted (Helin 1972) The T change is most sensitive to hypoxia of the cardiac muscle but at the same time least specific while the situation with the Q and QS changes is opposite

The choice of the ECG changes to be used as criteria of IHD is in itself a problem. where should we set the limit? In the present work only relatively severe ECG changes were taken into account of the Q changes for example only the major Q changes (Minnesota code 1 1) and of the ST/T changes only the major ST/T" changes (Minnesota code 4 1 5 1 5 2) were observed

The ST/T changes in ECG have given rise to lively discussions among investigators Some consider the ST/T changes nonspecific either physiological or attributable to some other causes such as age (Sleeper and Orgain 1963 Rodstein et al 1966 Marriot 1967 Winsor 1968 Rotman et al 1972 Simonson 1972) while others regard the ST/T changes as being typical of ischemic heart disease mainly coronary disease (Friedberg and Zager 1961 Rose 1971 Short 1972)

According to the Framingham study (Higgins et al 1965) the subjects with a pathological isolated Q wave in their ECG had about threefold risk of dying a coronary death compared with the average the greater the Q wave the greater the risk Isolated negative T-waves carried a 5-fold increased risk of death and 3-fold increased risk of an incident of CHD"

Kimura and Nakayama (1972) made roughly similar observations in noting that ST depression + negative T wave were the ECG changes with the poorest prognosis Ostrander (1970) noted that even a minor negative T wave impairs the prognosis of both women and men

The ST/T changes in postprandial ECG were discussed in the work of Ostrander and Weinstein (1964) which covered 30 healthy men aged 22 66 and 23 men with coronary disease aged 39 - 86 All the postprandial ECGs of healthy subjects showed a depression of the T wave compared with the ECG recorded before glucose administration and 19 coronary patients out of 23 appeared to have the same change Three healthy men further developed postprandial ST/T changes codable as pathological according to the Minnesota code It should be borne in mind however that the ST/T changes noted in all the three cases were less severe than those recorded in the present study and would not have been coded as pathological in this work

The present findings indicate that men have a roughly equal number of ECG changes at both low and high blood sugar values For example the subjects with a 2-hour blood glucose value ranging within 30-78 mg/100 ml had as many ECG changes as the subjects with a blood glucose level of 112 132 mg/100 ml and those with a level of 132 350 mg/100 ml The situation in the female series was similar

It can therefore be assumed that the time of recording ECG relative to the glucose tolerance test was not responsible for false positive ST/T changes

ECG as an indicator of IHD

In most mass screening surveys of the epidemiology of IHD the criteria of IHD have included not only certain ECG changes but also anamnestic angina pectoris syndrome and anamnestically verifiable myocardial infarction (Dawber et al 1957 Epstein et al 1965 Welborn et al 1969 Bengtsson 1973 a Bengtsson et al 1973 b) Angina pectoris however is a subjective symptom and does not necessarily indicate the presence of ischemic heart disease The intention of the present work was to construct an objective indicator of IHD which would be applicable to

age groups of women than in those of men It also appears that patholog-ical ECG findings increase evenly along with age in the female series while in the male series the prevalence of positive ECG changes remains static from the age of 45 onwards

A majority of the ECG changes in women are ST/T changes no patholog ical Q changes were noted in women aged under 50 The ST/T changes in women increase evenly along with age

In the male series Q changes already appear in the youngest age group increasing steadily with age Q changes account for appr one fifth of the pathological ECG changes of men The ST/T changes of men increase sharply as we move from the youngest age group to the next whereafter their prevalence remains unchanged

The ECG changes other than Q or ST/T changes noted in the present work are of no great significance they accounted for 0 3 % of all changes in women and 0 8 % in men

The present prevalence of pathological ECG findings was nearly three-fold in the male series and over sixfold in the female series compared with the Framingham study (Higgins et al 1965) which covered people of the same age and employed similar criteria Compared with the Tecumseh study (Ostrander et al 1965 a) the present prevalence of pathological ECG in the male series was nearly threefold and that in the female series about eightfold When the Australian Busselton study (Welborn et al 1969) is used as reference the present ECG finding in men is about three-fold and that of women about tenfold

Compared with the studies conducted by Pyörälä et al (1973) in dif ferent parts of Finland the present prevalence of ECG findings is about twofold in the male series and about 2 5-fold in the female series Pyö-rälä s work showed the frequency of ST/T changes in women to be over two fold compared with those in men An interesting detail in Pyörälä s findings might be pointed out here numerous ECG findings were found at

According to the investigations of Short and Stowers (1972) a ST depression of only 0 5 mm combined with a negative T wave is a sign of clear ischemic heart disease They call such a change a major ST/T change while depressions of 0 25 - 0 5 mm are termed minor changes which are also pathological and are usually due to either coronary disease or left ventricular hyperthrophy

Rose (1971) also emphasizes the minor ST/T changes of ECG on the basis of his studies He draws attention to the curious fact that so many coronary deaths and myocardial infarctions seem to be completely unexpected catastrophes he postulates that minor symptoms and minor ECG changes may occur in the years before these unexpected illnesses In a previous (1968) paper Rose pointed out that the prevalence of IHD is underestimated in mass screening surveys i e IHD is more common in reality than is shown by the prevalence figures

Raftery et al (1971) found that coronary patients may have a patholog-ical ECG on certain occasions while at some other time the ECG may be normal which means that the ECG changes indicative of coronary disease may vary Accordingly ST/T changes once noted bear a great significance as indicators of ischemic heart disease

Many authors thus emphasize the role of even minor ST/T changes (0 25 0 5 mm depression of ST) as indicators of ischemic heart disease The ST/T changes interpreted as pathological in the present work were more serious

ECG finding

Attention is drawn to the great number of ECG changes although the criteria used in the interpretation were fairly strict Another finding which invites attention is the greater number of ECG changes in all the

This matter was mentioned by Punsar & Karvonen (1973) in discussing the relations between prevalence and incidence According to them two populations with the same prevalence of ECG changes need not have the same CHD incidence or mortality because the symptomatic stage of CHD may be different in different populations Hence in theory a low prevalence of ECG changes may be due to a short duration of CHD and a high prevalence of ECG changes may reflect a low mortality from the disease

Mekali (1976) noted that atherosclerosis of the coronary arteries is noticeably more common among men than women However it appears that the clinical symptoms and signs resulting from coronary artery stenosis occur in women at a lower degree of narrowing than in men

When discussing the frequency of ECG changes we must also bear in mind the great number of pensioners in the series investigated As many as 16 5 % of the men (125 men) were on pension of whom nearly a third (29 6 %) had ECG changes 8 5 % of the women (67 women) were on pension and almost examined represent the working age population the retirement on pension must have been due to some disease Taking into account the numerous ECG changes in the group of pensioners one can postulate heart disease as a common cause for retirement Anyway the high frequency of ECG findings among the pensioners increases the prevalence of pathological ECG in the whole series

Serum cholesterol

Cholesterol has been considered perhaps the most important risk factor of IHD both in men and in women aged below 50 (Giannini 1970 Kannel 1971 Stamler 1973) In women over 50 the significance of cholesterol as a risk factor of IHD is less clear (Kannel and Castelli 1972)

It has also been maintained that determination of the serum cholesterol level is the best simple means of estimating the risk of atherosclerotic

Merijärvi which is one of the neighbouring municipalities of Haapavesi where the present investigations were carried out At Merijärvi the prevalence of female T changes (Minnesota codes 5 1 - 5 3) was over 30 % the corresponding figure for men being nearly 15 % which values clearly exceed the prevalence of T changes noted in the present work It must be noted however that the ECG coding used by Pyörälä et al included changes of less severe degree than the coding in this investigation

According to the East West study (Punsar & Karvonen 1973) the prevalence of ECG changes in men was 5 7 % in the west and 6 7 % in the east at the beginning of the survey in 1959 Hence the present prevalence of male ECG changes was about twofold compared with the corresponding finding of the East West study It should be borne in mind however that the criteria of ECG coding differed somewhat in these two works

Why were there so many ECG changes? It is a well known fact that even experienced clinicians differ in their interpretation of ECG (Epstein et al 1961) but errors in interpretation can probably not explain the great number of ECG findings Nor does the effect of possible glucose intake appear an adequate explanation

It is known on the other hand that ischemic heart disease is exceptionally common in Finland Hence the pre stage of IHD might also be common some of the subjects suffering from such latent IHD develop clinical symptomatic ischemic heart disease while others do not develop it The great number of ECG findings might suggest that a large proportion of the population suffers from subclinical IHD

ECG findings were numerous in both sexes but were nearly twice as frequent in women as in men The ECG changes in women were however clearly milder which might be taken to indicate that the clinical manifestations of IHD are milder in middle aged women than men

blood pressure quintile (170 mmHg) and the two highest obesity quintiles When however the systolic blood pressure was below 170 mmHg high chol esterol together with obesity and overweight were not connected with pathological ECG in men

Serum triglycerides

The significance of triglycerides as a risk factor of IHD has been emphasized in several investigations over the last few years (e g Carlson & Böttiger 1972 Kannel & Castelli 1972)

The present studies showed that the women with exceedingly low tri glyceride values (0 2 0 8 mmol/l) had the same frequency of patholog ical ECGs as the women with high triglycerides (1 5 9 5 mmol/l)

Men on the other hand had fewer ECG changes in the lowest triglyc eride quintile than in the other four quintiles but the difference was not significant

In the female series the triglyceride values clearly increased along with age as it was earlier noted that the ECG changes increased along with age It could have been expected therefore that the number of pathological ECGs would have increased parallel with the rising tri glyceride values but this was not the case

The ECG-positive and the ECG-negative women did not differ in the mean triglyceride values The 22 men who had a Q wave (Minnesota code 1 1) signifying a necrotic change in their ECG however had a higher triglyceride mean (1 7 mmol/l) than the ECG-negative men (1 3)

Even in the tree analysis the role of triglycerides as a risk factor remained quite invisible in both the male and the female series in both sex groups the triglycerides only emerged at a late stage and no clear correlation appeared

disease particularly coronary disease (Stamler 1973)

In the present study cholesterol increased along with age parallel with the increase of the prevalence of pathological ECG It was noted however that the men with a cholesterol level of 155 - 232 mg/100 ml had the same frequency of pathological ECG findings as the men with a cholesterol level ranging from 306 to 456 mg/100 ml The situation in the female series was more or less similar no significant differences were noted in the frequency of pathological ECG whether the cholesterol level was low (89 224 mg/100 ml) or high (310 - 441 mg/100 ml) Nor did the ECG-positive and the ECG-negative subjects differ as regards mean cholesterol in either sex group Not even the subjects with a pathological Q change in their ECG had a cholesterol mean different from the corresponding mean of the ECG-negative subjects

The present work thus gave no evidence of a correlation between serum cholesterol and IHD when cholesterol was viewed as a single risk factor Werkö (1976) analyzed critically the findings of three comprehensive epidemiological studies (the Framingham Study the National Pooling Project and the Stockholm Prospective Study) and concluded that none of the risk factors is very important alone According to him the worst combination is that between smoking and hypertension or high cholesterol or both The study by Wilhelmsen et al (1973) similarly revealed hypertension high cholesterol and cigarette smoking to be a combination indicative of a high risk of myocardial infarction

In the present combination analysis (tree analysis) cholesterol was absent from all the branches of the tree analysis of women which means that none of the present methods showed cholesterol to be a risk factor of IHD in the female group In the male series cholesterol was clearly connected with the ECG variable together with high systolic blood pressure and obesity This correlation involved the highest cholesterol quintile (cholesterol 306 mg/100 ml)

blood pressure quintile (170 mmHg) and the two highest obesity quintiles When however the systolic blood pressure was below 170 mmHg high chol esterol together with obesity and overweight were not connected with pathological ECG in men

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Even in the tree analysis the role of triglycerides as a risk factor remained quite invisible in both the male and the female series In both sex groups the triglycerides only emerged at a late stage and no clear correlation appeared

Summarizing we can say that none of the present methods showed either triglycerides or cholesterol to be a risk factor of IHD in the female series In the male series too the correlation between triglycerides and IHD remained uncertain although the finding suggested that a high triglyceride level might correlate with severe IHD

Systolic and diastolic hypertension

Many of the earlier studies have shown conclusively that both sys tolic and diastolic hypertonia is a risk factor of IHD in both sexes (e g Stamler 1973 Kannel 1974) The importance of early and effective treatment of hypertonia is emphasized (Veterans Administration Co opera tion Study Group on Antihypertensive Agents 1970) although it has not been proved that treatment of hypertonia as such would definitely reduce coronary events

The present findings showed that the systolic and diastolic blood pressure of women and the systolic blood pressure of men increased along with age (40 59 yr) The diastolic pressure of men remained unchanged despite increasing age

It was further noted that the ECG positive women and men had higher systolic and diastolic blood pressure than the ECG negative subjects The difference in the diastolic pressure of men was not great however though it was statistically significant ($p < 0\ 05$)

When the relationship between hypertonia and IHD was examined in the different quintiles the highest blood pressure quintile was found to in clude more ECG-positive men and women than the lowest quintile A sig- nificant ($p < 0\ 05$) difference was only noted between the systolic pres sures of women The proportion of ECG-negative women increased evenly along with elevation of both systolic and diastolic blood pressure no similar trend was noted in the male series for only the highest blood

pressure quintile (170-250/100-140) was found to contain more ECG-findings than the other quintiles

Women were found to have a clearly higher ($p < 0.001$) mean systolic blood pressure than men while the mean diastolic pressure was of the same order in the two groups Since women also had more ECG changes than men it can be surmised that the ECG findings of women are partly explained by the higher blood pressure The significance of blood pressure is suggested by the fact that women had more ECG changes than men at the same blood pressure value (fig 4 5)

It should also be borne in mind however that the lowest blood pressure quintile included relatively many ECG-positive subjects in both sex groups The female group with low blood pressure (95-140 mmHg) included a major proportion of ECG-positive subjects or 20 8 % (the proportion of ECG-positive women in the total series was 26 5 %) Correspondingly the lowest diastolic pressure quintile (60-80 mmHg) included 20 1 % ECG-positive women

The situation in the male series was more or less similar when systolic blood pressure was low (105-135 mmHg) ECG-positive subjects accounted for 13 1 % (the proportion of ECG-positive men in the total male series was 14 3 %) and when diastolic pressure was low (60-80 mmHg) the percentage of ECG-positive men was also high 14 4 %

In the tree analysis the role of systolic blood pressure appeared very clearly in both sex groups In the total female series pathological ECG was accompanied by high systolic blood pressure age over 50 heavy work or retirement and the lowest obesity quintiles In the group of women aged under 50 systolic blood pressure was the only risk factor and if the subject belonged to one of the lowest three blood pressure quintiles (systolic blood pressure ≤ 165 mmHg) no other risk factors emerged In the group of hypertonic women aged over 50 ECG change

correlated with office and standing work no further explanation was provided by the tree analysis

In men high systolic blood pressure was closely associated with the ECG variable together with obesity and high cholesterol In the group of retired men however high systolic blood pressure did not explain the incidence of pathological ECG

The role of diastolic blood pressure was small in the tree analysis of both sex groups it appeared only at the last few branches and provides no ground for conclusions

The present findings suggest that systolic blood pressure is the most important risk factor of IHD in women being the only risk factor in women under 50 years old IHD and systolic blood pressure also clearly correlate in the male group and systolic hypertension is further accompanied by obesity and high cholesterol No firm conclusions can be drawn concerning diastolic blood pressure in either sex group

Diabetes mellitus and glucose intolerance

A clear correlation between depressed glucose tolerance and IHD has been noted in both women and men by several investigators (e g Kannel et al 1967 a Stamler and Epstein 1972) According to the Framingham report (Garcia et al 1970) CHD was particularly frequent in women taking insulin but it has also been found to correlate with milder forms of diabetes (Weaver et al 1970) Yet many authors consider diabetes mellitus and depressed glucose tolerance a secondary risk factor of CHD (Simborg 1970 Stamler 1973)

The present study revealed that the mean 2 hour glucose value was higher ($p < 0\ 001$) in women than in men and that this mean clearly ($p < 0\ 001$) increased along with age in both sexes Since it was earlier demonstrated (fig 1) that the prevalence of pathological ECG

increased along with increasing age it could be expected that it would also increase along with rising 2 hour glucose value but this was not the case All the glucose quintiles contained equal numbers of ECG-positive subjects in both sex groups Nor did the 2 hour glucose means differ in the sex groups

If we further examine the glucose quintiles (fig 6) we can see that the proportion of ECG changes was essentially the same regardless of whether the 2 hour blood glucose value was low (quintile 1) moderate (quintile 3) or high (quintile 5) In other words the low or high level of blood glucose has no effect on the ECG finding

The women with a pathological Q wave in their ECG (Minnesota code 1 1) had a clearly higher 2 hour mean of blood glucose than the ECG-negative women But as there were only 6 such women no conclusions can be drawn

In the tree analysis depressed glucose tolerance only appeared in the group of women on pension whereas the male group appeared to be unaffected by it

Overweight and obesity

Contradictory views have been presented concerning the correlation between overweight and obesity on the one hand and IHD on the other Obesity has been assumed to correlate with angina pectoris and sudden deaths due to arrythmia but its relation to coronary disease has been unclear (e g Kannel et al 1967 b Heyden et al 1971)

The women taking part in the present investigation were relatively fat and the men relatively thin (table 11) The height weight and skinfold measurements of the ECG-positive and the ECG-negative subjects did not differ in either sex group

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The women taking part in the present investigation were relatively fat and the men relatively thin (table 11) The height, weight and skinfold measurements of the ECG-positive and the ECG-negative subjects did not differ in either sex group

correlated with office and standing work no further explanation was provided by the tree analysis

In men high systolic blood pressure was closely associated with the ECG variable together with obesity and high cholesterol In the group of retired men however high systolic blood pressure did not explain the incidence of pathological ECG

The role of diastolic blood pressure was small in the tree analysis of both sex groups it appeared only at the last few branches and provides no ground for conclusions

The present findings suggest that systolic blood pressure is the most important risk factor of IHD in women being the only risk factor in women under 50 years old IHD and systolic blood pressure also clearly correlate in the male group and systolic hypertension is further accompanied by obesity and high cholesterol No firm conclusions can be drawn concerning diastolic blood pressure in either sex group

Diabetes mellitus and glucose intolerance

A clear correlation between depressed glucose tolerance and IHD has been noted in both women and men by several investigators (e g Kannel et al 1967 a Stamler and Epstein 1972) According to the Framingham report (Garcia et al 1970) CHD was particularly frequent in women taking insulin but it has also been found to correlate with milder forms of diabetes (Weaver et al 1970) Yet many authors consider diabetes mellitus and depressed glucose tolerance a secondary risk factor of CHD (Simborg 1970 Stamler 1973)

The present study revealed that the mean 2 hour glucose value was higher ($p < 0\ 001$) in women than in men and that this mean clearly ($p < 0\ 001$) increased along with age in both sexes Since it was earlier demonstrated (fig 1) that the prevalence of pathological ECG

blood pressure quintile In the male series the ECG variable was associated with the thin subjects rather than the obese ones

Thinness as a risk factor was thus associated in both sexes with occupation while obesity together with high systolic blood pressure and high cholesterol was a risk factor of men The obesity of women did not correlate clearly with the ECG variable

Smoking

The proportion of smokers in the male series was 58 2 % In the East-West study (Key et al 1967) 68 5 % of the eastern men and 57 2 % of the western men smoked cigarettes When the ex-smokers are included altogether 83 1 % of the present male subjects are smokers (58 2 % + 24 9 %) The corresponding value in the Norwegian series investigated by Zeiner-Henriksen (1976) was of the same order 78 % The proportion of smokers is similar in all age groups while ex smokers are more numerous in the oldest age group (54 59 yr) than in the others and non-smokers less numerous in that group than in the others

Only 12 4 % of the women were smokers and 6 5 % ex smokers totalling 18 9 % The corresponding value in Zeiner Henriksen s series (1976) was 25 % The proportions of smokers were similar in the different age groups of women

The correlation between smoking and IHD was clearly visible in the youngest group of men (40 44 yr) where the non-smokers included only 1 9 % ECG-positive men The proportion of ECG-positive smokers and ex-smokers was over 9 % (9 3 % and 9 5 %) This difference is highly significant It should further be pointed out that there were 53 non-smoking men in this age group and only one of them had pathological ECG In the ne t age group (45 49 yr) ECG changes were equally numerous in all the different smoking groups but in the group aged 50 54 ex-smokers had

The women who were considerably obese and had marked overweight had more ECG changes than the others but the difference was not statistically significant

The ECG changes of men were equally numerous in all the quintiles regardless of the structural type

According to several investigations (e g Stamler et al 1966 Keys et al 1972) obese subjects are more inclined to hypertonia diabetes and hyperlipidemia than thin ones and hence obesity correlating with several other risk factors constitutes a marked risk The observations of both Stamler (1967) and Kannel et al (1971) *showed the progressive and apparently synergistic effect of the presence of two three or four risk factors*

Both the thin and the fat subjects of the obesity group play a conspicuous role in the present multivariate analysis In the female series *one risk group consisted of thin hypertonic women aged over 50* doing heavy work or household work In the male series the obesity correlated most strongly with the ECG variable after exclusion of the subjects on pension In the male series obesity was generally associated *with pathological ECG together with high systolic blood pressure and high cholesterol It was significant however* that men who were thin or normal on the basis of their skinfolds and who were doing heavy or stationary work made up a risk group of their own No other risk factors were combined with this correlation in the analysis

The overweight variable only pertains to the working subjects when the subjects on pension were included in the tree analysis this variable did not appear in either sex group After the exclusion of retired subjects too *the contribution of overweight as a correlating factor seems quite small* In the female series the overweight variable was associated with high triglycerides and the highest diastolic

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the series examined considerably less than men

In the present work the correlation between IHD and smoking was clearly apparent in the youngest age group of men and in the group of men on pension which means that the present finding agrees with the results of the previous studies of incidence and mortality The present findings yielded no evidence of any correlation between IHD and smoking in women

Occupation

In both sexes the largest occupational group consisted of subjects doing heavy manual work they accounted for 56 2 % of women and 66 2 % men The women in this group were generally wives of small farmers whose household chores were supplemented by heavy work in cattle raising The men did normal agricultural work and additional lumbering in the winter for further earnings

The second largest group of women consisted of those doing only household work which may often be quite heavy they accounted for 21 2 % of the women The third largest female group was that of pensioners 8 5 % and next came the women doing standing" work i e shop assistants waitresses nurses etc who accounted for 6 5 % 4 7 % of the women were doing office work and the smallest group consisted of 23 teachers shopkeepers etc accounting for 2 9 %

The second largest group of men was that of pensioners (16 5 % or 125 subjects) following the subjects with heavy manual work Thus every sixth of the 761 men aged 40 59 was on pension for some disease or reason The other male groups were clearly smaller group 2 (teacher salesman shopkeeper etc) 53 subjects or 7 % group 3 (office work car transport service etc) 44 subjects or 5 8 % The smallest male groups were group 4 (waiter shop assistant and other standing work) consisting of 17 subjects or 2 3 % of all men and group 5 (household

clearly more ECG changes than the others This can be a coincidence or it may mean that smoking had been given up either spontaneously or at the doctor s advice when the IHD symptoms appeared Taking into account all the age groups ECG changes were most numerous among ex smokers and least numerous among non-smokers (18 2 % and 10 4 %) but the difference was not quite significant

The ECG changes of women were most numerous in the group of non smokers and least numerous in the group of smokers but no significant differences appeared (27 6 % and 21 0 %) In the group aged 50 - 54 non-smokers had highly significantly more ECG changes than smokers or ex smokers it must be pointed out however that women were generally few in the groups of smokers and ex smokers and that this age group for example included 27 smokers and 12 ex smokers

The smokers were further divided into groups on the basis of the quality of smoking and the number of cigarettes consumed There were no cigar smokers and all the pipe smokers were men ECG-positive and ECG-negative subjects were equally numerous in all the smoking groups of both women and men The age groups were not specified in this analysis but the whole series was treated as one unit

The tree analysis did not reveal smoking at all in the female series and in the male series it appeared only in the group of pensioners where it seemed to correlate strongly with the ECG variable

Having reviewed the findings of three comprehensive epidemiological studied Werkö (1976) concludes that smoking together with high blood pressure is the most important risk factor of IHD The IHD mortality of men has also been clearly connected with smoking in most studies (e g Punsar and Pyörälä 1970 Zeiner Henriksen 1976) No equally clear evidence is so far available for the relation between IHD and smoking in women The reason for this may be that women smoke or have smoked in

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work (e.g. car transport service) constituted a risk group without any other correlating factors The thin women doing heavy manual work or household work also made up a risk group of their own but this chain of correlations was supplemented by high systolic blood pressure (165 mmHg) and age over 50 Also age over 50 and hypertonia were linked with occupational groups 3 and 4 (office work standing work e g shop assistants and waitresses) in the female series Attention is further invited to the fact that the female group 2 (teacher stress job) has been left out of the correlations entirely this group however included only 23 subjects as it was pointed out above

Several earlier investigations have shown that CHD and inactive occupation are correlated (e g Morris et al 1953 Wilhelmsen and Tibblin 1971) Conversely a correlation has also been established between heavy work and CHD (Karvonen et al 1972) Poor social conditions (low social class low income level low educational level social alcohol problems) have also been found to be associated with in increased frequency of myocardial infarctions and sudden deaths (Werkö 1976) The present findings suggest that heavy work and IHD are correlated but it must be taken into account that more than half of the present subjects of both sexes did heavy manual work It should further be emphasized that the number if pensioners in the series is great about every 6th man and about every 12th woman were on pension because of some disease or other reason and the groups of pensioners of both sexes had the most ECG changes

work) comparising 15 subjects or 2 0 %

ECG changes were most numerous in the groups of pensioners of both sexes 43 4 % of the female pensioners (29) and 29 6 % of the male pensioners (37) had pathological ECG findings

The concentration of ECG changes in the group of pensioners seems natural for it can be assumed that a large proportion of these subjects had retired because of cardiovascular defects Also the high proportion of pensioners in the total series and the numerous ECG findings made among them explain the great number of ECG changes in the whole series

The second highest frequency of ECG changes was recorded for the groups of men and women doing household work In the female series however the group doing heavy manual work (group 1) had almost equally many ECG findings It can be postulated that the men in the household group have taken up lighter work of this kind being unable to do heavier work because of IHD or other symptoms and being not yet granted a pension It must be remembered however that this group includes only 15 men

The other occupational groups of men have roughly equal proportions of ECG changes One further point of interest group 2 of women (teacher shokeeper stress job) contains only the pathological ECG change this groups does not however include more than 23 women Moreover most (20) of the women in group 2 are under 50 years old

The role of occupation was clearly visible in the tree analyses In both sexes the ECG variable correlated strongly with the group pen sioners although these subjects had not retired particularly because of IHD Anyway ECG changes were most numerous in the group of pen sioners among both men and women

When the pensioners were excluded from the analysis the role of occupation appeared clearly thin or normal men doing heavy or stationary

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CONCLUSIONS

The results obtained by using the present methods give rise to the following conclusions

- The prevalence of IHD was very great in both men and women when accept ECG changes were used as the criteria of IHD Women had more IHD than men in all age groups but the IHD of men seemed to be a more severe kind on the basis of the Q changes
- Systolic hypertension was the most important risk factor of IHD in the female series being the only risk factors in the group of women under 50 In the male series systolic hypertension was not an independent risk factor but it correlated clearly with IHD together with obesity and high cholesterol
- Smoking appeared clearly as in independent risk factor in the youngest (40 - 44 yr) group of men No other age groups of men had smoking as a risk factor but in the group of pensioners smoking re appeared as a correlating factor of IHD In the female series smoking and IHD appeared to have no correlation
- Cholesterol did not emerge as a risk factor in the female series In the male series it was not an independent risk factor either but was associated with IHD together with obesity and high systolic blood pressure
- Each sex had a risk group for occupation and IHD 1) thin women over 50 doing heavy manual work or household work with systolic blood pres sure $\leq$ 165 mmHg 2) men who are thin or normal on the basis of their skinfolds and who do either heavy or stationary work

SUMMARY

In the spring 1971 a mass screening survey was carried out in the municipality of Haapavesi (7500 inhabitants) in Northern Finland All the women and men aged 40-59 years living within the municipality were invited to participate The examinations were attended by 761 men and 793 women making the percentage of participation 90 9 %

The correlation between ischemic heart disease (IHD) and the fol lowing risk factors was investigated serum cholesterol serum tri glycerides systolic and diastolic hypertension depressed glucose tolerance obesity and overweight as well as smoking and occupation

Electrocardiography alone was used as the indicator of IHD when the ECG changes were of relatively severe degree The subjects whose ECG was found to include one of the following changes according to the Minnesota code were classified as ECG-positive (pathological ECG) 1) Minnesota code 1 1 ("major Q) 2) Minnesota code 4 1 5 1 5 2 (major ST/T depression) 3) Minnesota code 6 1 (complete A V block) 7 1 (complete left bundle branch block) and 8 3 (atrial fibrillation)

The ECG-positive women numbered 210 accounting for 26 5 % of the total female series There were 202 ST/T changes (96 2 %) 6 Q changes (2 9 %) and 2 other changes (1 0 %)

The ECG positive men numbered 109 (14 3 %) of whom 22 (20 2 %) had Q changes 81 (74 3 %) ST/T changes and 6 (5 5 %) other changes

The women had more ECG changes than men in all the age groups but the ECG changes men were more severe than those of women

In the female series the frequency of pathological ECG changes clea ly nc eased along with increasing age while in the male series it inc eased from the youngest (40-44 yr) age group to the next (45-59 yr) From the age of 45 onwards the prevalence of pathological ECG remained unchanged in the male group

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- Systolic hypertension was the most important risk factor of IHD in the female series being the only risk factors in the group of women under 50 In the male series systolic hypertension was not an independent risk factor but it correlated clearly with IHD together with obesity and high cholesterol

Smoking appeared clearly as in independent risk factor in the youngest (40 44 yr) group of men No other age groups of men had smoking as a risk factor but in the group of pensioners smoking re-appeared as a correlating factor of IHD In the female series smoking and IHD appeared to have no correlation

Cholesterol did not emerge as a risk factor in the female series In the male series it was not an independent risk factor either but was associated with IHD together with obesity and high systolic blood pressure

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The correlations between the different risk factors and IDH were examined by dividing the men and women into quintiles on the basis of the numerical value of each risk factor and by recording the proportion of pathological ECGs in each quintile Moreover the mutual correlations between IHD and the different risk factors were analyzed by means of tree analysis

The following results were obtained for the correlations between IHD and the different risk factors

1 Cholesterol

In the female series cholesterol and IHD did not correlate at all In the male series cholesterol did not emerge as an independent risk factor either but was associated with IHD together with systolic hypertension and obesity

2 Triglycerides

The women showed no clear correlation between triglycerides and IHD The men had a correlation when IHD was very severe

3 Hypertension

Systolic hypertension was clearly the most important risk factor of IHD in the female series being the only risk factor in the women aged under 50 In the male series too systolic hypertension and IHD clearly correlated though the correlation was not equally distinct to that in the female series In the male series a chain of correlations consisted of systolic hypertension obesity and high cholesterol

The significance of diastolic blood pressure was overshadowed by systolic blood pressure in each sex group

4 Depressed glucose tolerance

Depressed glucose tolerance did not correlate clearly with IHD in either sex group

5 Overweight and obesity

Overweight and IHD did not correlate clearly in either sex group The obesity variable and IHD however exhibited some correlations 1) thin hypertonic women aged over 50 doing heavy manual work or household work 2) thin or normal men doing heavy or stationary work and 3) obese men with high systolic blood pressure (≥ 170 mmHg) and high cholesterol (≥ 306 mg/100 ml)

6 Smoking

Smoking and IHD did not seem to correlate in the female series

In the male series smoking emerged as an independent risk factor in the group of the youngest men (40–44 yr) and another time though not so markedly in the group of pensioners

7 Occupation

The correlation between occupation and IHD appeared in both sex groups see point 5 It should still be emphasized that thin men doing heavy or stationary work constituted a risk group without any other correlating factors

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Heikki Juustila

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REFERENCES

American Heart Association Committee on electrocardiography recommendations for standardisation of leads and of specifications for instruments in electrocardiography and vectorcardiography Circulation 1967 35 583

Aronow W S Kaplan M A & Jacob D Tobacco a precipitating factor in angina pectoris Ann Intern Med 1968 69 529

Aronow W S & Rokaw S N Carboxyhemoglobin caused by smoking non nicotine cigarettes Effect in angina pectoris Circulation 1971 44 782

Aronow W S & Swanson A J Non nicotinized cigarettes and angina pectoris Ann Intern Med 1969 70 1227 (a)

Aronow W S & Swanson A J The effect of low nicotine cigarettes on angina pectoris Ann Intern Med 1969 71 599 (b)

Ball K & Turner R Smoking and the heart the basis for action Lancet 1974 2 822

Bengtsson C Ischaemic heart disease in women Acta med scand 1973 suppl 549 (a)

Bengtsson C Blood pressure in a population sample of women and in women with ischaemic heart disease Acta med scand 1973 suppl 549 40 (b)

Bengtsson C Physical activity in a population sample of women and in women with ischaemic heart disease Acta med scand 1973 suppl 549 93 (c)

Bengtsson C Smoking habits in a population sample of women and in women with ischaemic heart disease Acta med scand 1973 suppl 549 60 (d)

Bengtsson C Social factors stress experience and personality traits in women with ischaemic heart disease compared to a population sample of women Acta med scand 1973 suppl 549 82 (a)

Bengtsson C Björntorp P & Tibblin E Serum cholesterol and serum tri glyceride levels in a population sample of women and in women with ischaemic heart disease Acta med scand 1973 suppl 549 51 (a)

Bengtsson C Blohmé G Hallberg L Hällström T Isaksson B Korsan-Bengtsen K, Rybo G Tibblin E Tibblin G & Westerberg H The study of women in Gothenburg 1968-1969 a population study General design purpose and sampling results Acta med scand 1973 193 311 (b)

Bengtsson C Blohmé G & Waldenström J Diabetes mellitus carbohydrate tolerance and early insulin response to an intravenous glucose injection in a population sample of women and in women with ischaemic heart dis ease Acta med scand 1973 suppl 549 65 (c)

Blackburn H Classification of the electrocardiogram for population studies Minnesota code J Electrocardiology 1969 2(3) 305

Blackburn H Keys A Simonson E Rautaharju P & Punsar S The electro cardiogram in population studies A classification system Circulation 1960 21 1160

Bolander A M A comparative study of mortality by cause in four nordic countries 1966-1968 with special reference to male excess mortality Statistical reports 1971 Be 1971 9 National Central Bureau of Sta t stics Stockholm 1971

Brown D F Blood lipids and lipoproteins in atherogenesis Amer J Med 1969 46 691

Brunner D & Manelis G Physical activity at work and ischemic heart disease In book Coronary heart disease and physical fitnes Edited by O Andrée Larsen and R O Malmborg Munksgaard Copenhagen 1971

Carlson L A & Böttiger L E Ischaemic heart disease in relation to fasting values of plasma triglycerides and cholesterol Stockholm pro spective study Lancet 1972 1 365

Cassel J Hill C Heyden S Bartel A G Kaplan B H Tyroler H A Cornoni J C & Hames C G Occupation and physical activity and coronary heart disease Arch intern Med 1971 128 920

Chapman J M Coulson A H Clark V A & Borun E R The differential effect of serum cholesterol blood pressure and weight on the incidence of myo cardial infarction and angina pectoris J chron Dis 1971 23 631

Chapman J M Goerke L S Dixon W Loveland D E & Phillips E The clini cal status of a population group in Los Angeles under observation for two or three years Amer J publ Hlth 1957 47 33

Chapman J M & Massey F J The interrelationship of serum cholesterol hypertension body weight and risk of coronary disease results of the first ten years follow-up in the Los Angeles heart study J chron Dis 1964 17 933

Chiles R & Tzagournis M Excessive serum insulin response to oral glu cose in obesity and mild diabetes Study of 501 patients Diabetes 1970 19 458

Cotton S G Nixon J M Carpenter R G & Evans D W Factors discrimina ting men with coronary heart disease from healthy controls Brit Heart J 1972 34 458

Dawber T R Kannel W B & McNamara P M The prediction of coronary heart disease Trans Assoc Life In Med Dir Amer 1963 47 70

Dawber T R Moore F E & Mann C V Coronary heart disease in the Framingham study Amer J publ Hlth 1975 47 4

Doll R & Hill A B Mortality in relation to smoking ten years observations of British doctors Brit Med J 1964 1 1399 & 1467

Doyle J T Dawber T R Kannel W B Kinch S H & Kahn H A The relationship of cigarette smoking to coronary heart disease The second report of the combined experience of the Albany NY and Framingham Mass studies J Amer Med As oc 1964 190 886

Doyle J T Heslin A S Hilleboe H E & Formel P F Early diagnosis of ischaemic heart disease New Engl J Med 1959 261 1096

Epstein F H The epidemiology of coronary heart disease A review J chron Dis 1965 18 735

Epstein F H Hyperglycemia A risk factor in coronary heart disease Circulation 1967 36 609 (a)

Epstein F H Predicting coronary hea t disease JAMA 1967 201 175 *(b)*

Epstein F H Doyle J T Pollack A A Pollack H Robb G P & Simonson E Observer interpretation of electrocardiograms Suggestions for objective interpretations J Ame med Ass 1961 175 847

Epste n F H & Kruege D E The changing incidence of coronary heart disease In book Modern trends in cardiology Vol 2 By A Morgan Jones Butterwo ths London 1969

Epstein F H Ostrander Jr L D Johnson B C Payne M W Hayner N S Keller J B & Francis Jr T Epidemiological studies of cardiovascular disease in a total community - Tecumseh Michigan Ann intern Med 1965 62 1170

Fox S M & Haskell W L Physical activity and health maintenance J Rehab 1966 32 89

Frank C W Weinblatt E Shapiro S & Sager R V Myocardial infarction in men role of physical activity and smoking in incidence and mortality J Amer Med Assoc 1966 198 1241

Frank C V Weinblatt E Shapiro S & Sager R V Physical inactivity as a lethal factor in myocardial infarction among men Circulation 1966 36 1022

Friedberg C K & Zager A Nonspecific ST and T wave changes Circulation 1961 23 655

Froelicher V F & Oberman A Analysis of epidemiological studies of physical inactivity as risk factor for coronary artery disease Progr cardiovasc Dis 1972 15 41

Garcia M J Gordon T McNamara P M & Kannel W B Morbidity and mortality in diabetics and a general population Sixteen year follow-up experience in the Framingham study Diabetes 1970 19 suppl 1 375

Gertler M M & White P D Coronary heart disease in young adults a multidisciplinary study Cambridge Harward University Press 1954

Giannini S D Coronary risk factors Arq Bras Cardiol 1970 23 345

Gordon T Kannel W B McGee D & Dawber T R Death and coronary attacks in men after giving up cigarette smoking Lancet 1974 2 1345

Gordon T & Kannel W B Predisposition to atherosclerosis in the head heart and legs The Framingham study JAMA 1972 221 661

Hagerup L M Coronary heart disease ri k factors in men and women Acta med scand 1973 suppl 557

Hammond E C Smoking in relation to death rates of 1 million men and women in National Cancer Institute Monograph No 19 pp 127 204 U S Government Printing Office Washington DC 1966

Hekali P Coronary angiography and clinical symptomatology Academic dissertation Helsinki 1976

Helin M Elektrokardiografia koronaaritaudissa Duodecim 1972 88 1324

Herman M V & Gorlin R edit Premature coronary artery disease and the preclinical diabetic state Amer J Med 1965 38481 483

Heyden S Cassel J C Bartel A Tyroler H A Hames C G & Cornoni J C Body weight and cigarette smoking as risk factors Arch intern Med 1971 128 915

Higgins I T T Kannel W B and Dawber T R The electrocardiogram in epidemiological studies Reproducibility validity and international comparision Brit J prev soc Med 1965 19 51

Hill P & Wynde E L Smoking and cardiovascular disease Amer Heart J 1974 4 491

Hurst J W Coronary artery disease Introduction and classification In book The heart arteries and veins ed by J W Hurst R B Logue R C Schlant & N K Wenger *Copyright by McGraw Hill Inc 1974 p 985*

Hyvärinen A & Nikkilä E A Specific determination of blood glucose with o toluidine Clin chim Acta 1962 7 140

Inter-society commission for heart disease resources Atherosclerosis study group and epidemiology study group primary prevention of the atherosclerotic diseases Circulation 1970 42 A 55

Jackson W P U Goldberg M D Marine N & Vinik A I Effectiveness reproducibility and weight relation of screening test for diabetes Lancet 1968 2 1101

Kannel W B Lipid profile and the potential coronary victim Amer J clin Nutr 1971 24 1074

Kannel W B Role of blood pressure in cardiovascular morbidity and mortality Progr cardiovasc Dis 1974 17 5

Kannel W B & Castelli W P The Framingham study of coronary heart disease in women Med Tms (N Y) 1972 100 173

Kannel W B Castelli W P Gordon T & McNamara P Serum cholesterol lipoproteins and the ri k of coronary heart disease The Framingham study Ann intern Med 1971 74 1 (a)

Kannel W B Castelli W P & McNamara P M The coronary profile twelwe year follow-up in the Framingham study J occup Med 1967 9 611 (a)

Kannel W B Dawber T R Kagan A Revotskie N & Stokes J Factors of risk in the development of coronary heart disease - six year follow- The Framingham study Ann intern Med 1961 55 33

Kannel W B Dawber T R & McNamara P M Detection of the coronary-prone adult The Framingham study J Iowa med Soc 1966 56 26

Kannel W B Dawber T R & Revotskie N Epidemiology of coronary heart disease Geriatrics 1962 17 675

Kannel W B Garcia M J McNamara P M & Pearson G Serum lipid precursors of coronary heart disease Hum Path 1971 2 129 (b)

Kannel W B LeBauer J T Dawber T R & McNamara P M Relation of body weight to development of coronary heart disease The Framingham study Circulation 1967 35 734 (b)

Karvonen M J Tupakanpoltto ja koronaaritauti Duodecim 1972 88 1283

Karvonen M J Blomqvist G Kallio V Orma E Punsar S Rautaharju P Takkunen J & Keys A Epidemiological studies related to coronary heart disease characteristics of men aged 40-59 in seven countries C 4 Men in rural east and west Finland Acta med scand 1967 suppl 460 169

Karvonen M J Nygård K & Punsar S Coronary heart disease in lumber jacks Scand J clin Lab Invest 1972 29 suppl 122 13

Karvonen M J Orma E Punsar S Kallio V Arstila M Luomanmäki K & Takkunen J Coronary heart disease in seven countries VI Five year experience in Finland Circulation 1970 41 suppl I 52

Keys A (edit) Coronary heart disease in seven countries Circulation 1970 41 suppl I

Keys A A a anis C Blackburn H W van Buchem F S P Buzina R Djordjević B S Dontas A S Fidanza F Karvonen M J Kimura N Lekos D Monti M

Puddu V & Taylor H L Epidemiological studies related to coronary heart disease characteristics of men aged 40 59 in seven countries Acta med scand 1967 suppl 460

Keys A Aravanis C Blackburn H W van Buchem F S P Buzina R Djordjević B S Fidanza F Karvonen M J Menotti A Puddu V & Taylor H L Coronary heart disease overweight and obesity as risk factors Ann intern Med 1972 77 15

Keys A Taylor H L Blackburn H W Brozek J Anderson J T & Simonson E Coronary heart disease among Minnesota business and professional men followed fifteen years Circulation 1963 28 381

Khosla T & Lowe C R Indices of obesity derived from body weight and height Brit J prev soc Med 1967 21 122

Kimura N & Nakayama Y Natural history of heart disease from epidemiological investigation Japan circul J 1972 36 11

Krikler D M & Macfarlane P W Standards for electrocardiographs Brit Heart J 1974 36 945

Krotkievski A Nowotna Walcova R & Toppercer A Latent coronary insufficiency in diabetics Pol med J 1970 9 73

Lal H B & Bahl A L Association of diabetes mellitus hypertension and coronary heart disease Indian Heart J 1967 19 96

Lehtovirta E Obesity in relation to glucose tolerance A cross sectional anthropometric and retrospective study on Helsinki policimen Ann clin Res 1973 vol 5 suppl 10

Marble A Coronary artery disease in the diabetic Diabetes 1955 4 290

Marriott H J L Normal electrocardiographic variants simulating ischaemic heart disease JAMA 1967 199 103

McDonough J R Hames C G Stulb S C & Garrison G E Coronary heart dis ease among negroes and whites in Evans County Georgia J chron Dis 1965 18 443

McGill Jr H D (edit) Geography pathology of atherosclerosis Baltimore Maryland Williams & Wilkins 1968

Miettinen M Keski ikäisten miesten kuolleisuus sydämen sepelvaltimo tauteihin Suomessa 1965 Sos lääket aikak 1 1969 7 174

Miettinen M Sydämen sepelvaltimokuolleisuus Suomessa ja Ruotsissa Sos lääket aikak 1 1971 9 37

Miettinen T A Diabeettinen aihneenvaihdunta Duodecim 1971 87 87

Morris J N Heady J A Raffle P A B Roberts C G & Parks J W Coronary heart disease and physical activity of work Lancet 1953 2 10 & 1111

Morris J N Kagan A Pattison D C Gardner M J & Raffle P A B Inci dence and prediction of ischaemic heart disease in London busmen Lancet 1966 2 553

Mulcahy R Hickey N & Maurer B Coronary heart disease in women Study of risk factors in 100 patients less than 60 years of age Circulation 1967 36 577

Mulcahy R Hickey N & Maurer B Coronary heart disease A study of risk factors in 400 patients under 60 years Geriatrics 1969 24 106

Nikkilä E A Seerumin lipidit lipoproteiinit ja koronaaritauti Duo decim [illegible]

Puddu V & Taylor H L Epidemiological studies related to coronary heart disease characteristics of men aged 40-59 in seven countries Acta med scand 1967 suppl 460

Keys A Aravanis C Blackburn H W van Buchem F S P Buzina R Djordjević B S Fidanza F Karvonen M J Menotti A Puddu V & Taylor H L Coronary heart disease overweight and obesity as risk factors Ann intern Med 1972 77 15

Keys A Taylor H L Blackburn H W Brozek J Anderson J T & Simonson E Coronary heart disease among Minnesota business and professional men followed fifteen years Circulation 1963 28 381

Khosla T & Lowe C R Indices of obesity derived from body weight and height Brit J prev soc Med 1967 21 122

Kimura N & Nakayama Y Natural history of heart disease from epidemiological investigation Japan circul J 1972 36 11

Krikler D M & Macfarlane P W Standards for electrocardiographs Brit Heart J 1974 36 945

Krotkievski A Nowotna Walcova R & Toppercer A Latent coronary insufficiency in diabetics Pol med J 1970 9 73

Lal H B & Bahl A L Association of diabetes mellitus hypertension and coronary heart disease Indian Heart J 1967 19 96

Lehtovirta E Obesity in relation to glucose tolerance A cross sectional anthropometric and retrospective study on Helsinki policimen Ann clin Res 1973 vol 5 suppl 10

Marble A Coronary artery disease in the diabetic Diabetes 1955 4 290

Marriott H J L Normal electrocardiographic variants simulating ischaemic heart disease JAMA 1967 199 103

McDonough J R Hames C G Stulb S C & Garrison G E Coronary heart disease among negroes and whites in Evans County Georgia J chron Dis 1965 18 443

McGill Jr H D (edit) Geography pathology of atherosclerosis Baltimore Maryland Williams & Wilkins 1968

Miettinen M. Keski ikäisten miesten kuolleisuus sydämen sepelvaltimotauteihin Suomessa 1965 Sos lääket aikak 1 1969 7 174

Miettinen M Sydämen sepelvaltimokuolleisuus Suomessa ja Ruotsissa Sos lääket aikak 1 1971 9 37

Miettinen T A Diabeettinen aihneenvaihdunta Duodecim 1971 87 87

Morris J N Heady J A Raffle P A B Roberts C G & Parks J W Coronary heart disease and physical activity of work Lancet 1953 2 10 & 1111

Morris J N Kagan A Pattison D C Gardner M J & Raffle P A B Incidence and prediction of ischaemic heart disease in London busmen Lancet 1966 2 553

Mulcahy R Hickey N & Maurer B Coronary heart disease in women Study of risk factors in 100 patients less than 60 years of age Circulation 1967 36 577

Mulcahy R Hickey N & Maurer B Coronary heart disease A study of risk factors in 400 patients under 60 years Geriatrics 1969 24 106

Nikkilä E A: Seerumin lipidit lipoproteiinit ja koronaaritauti Duodecim 1972 88 1271

Puddu V & Taylor H L Epidemiological studies related to coronary heart disease characteristics of men aged 40 59 in seven countries Acta med scand 1967 suppl 460

Keys A Aravanis C Blackburn H W van Buchem F S P Buzina R Djordjević B S Fidanza F Karvonen M J Menotti A Puddu V & Taylor H L Coronary heart disease overweight and obesity as risk factors Ann intern Med 1972 77 15

Keys A Taylor H L Blackburn H W Brozek J Anderson J T & Simonson E Coronary heart disease among Minnesota business and professional men followed fifteen years Circulation 1963 28 381

Khosla T & Lowe C R Indices of obesity derived from body weight and height Brit J prev soc Med 1967 21 122

Kimura N & Nakayama Y Natural history of heart disease from epidemiological investigation Japan circul J 1972 36 11

Krikler D M & Macfarlane P W Standards for electrocardiographs Brit Heart J 1974 36 945

Krotkievski A Nowotna Walcova R & Toppercer A Latent coronary insufficiency in diabetics Pol med J 1970 9 73

Lal H B & Bahl A L Association of diabetes mellitus hypertension and coronary heart disease Indian Heart J 1967 19 96

Lehtovirta E Obesity in relation to glucose tolerance A cross sectional anthropometric and retrospective study on Helsinki policimen Ann clin Res 1973 vol 5 suppl 10

Marble A Coronary artery disease in the diabetic Diabetes 1955 4 290

Palatsi I Feasibility of physical training after myocardial infarction and its effect on return to work morbidity and mortality Academic dis sertation Oulu 1976

Paul O Risks of mild hypertension A ten-year report Brit Heart J 1971 33 116

Paul O Lepper M H Phelan W H Dupertuis G W MacMillan A McKean H & Park H A longitudinal study of coronary heart disease Circulation 1963 28 20

Pearson S Stern S & McGavack T H A rapid accurate method for the determination of total cholesterol in serum Anal Chem 1953 25 813

Pell S & D Alonzo C A three year study of myocardial infarction in a large employed population JAMA 1961 175 463

Pesonen E Norio R & Sarna S Thickening in the coronary arteries in infancy as an indication of genetic factors in coronary heart dis ease Circulation 1975 51 218

Punsar S Tupakointi ja sepelvaltimotauti Suom Lääk-L 1971 26 27

Punsar S & Karvonen M J Angina pectoris and ECG abnormalities in relation to prognosis of coronary heart disease in population studies in Finland Adv Cardiol 1973 8 148

Punsar S & Pyörälä K Cigarette smoking and the risk of death from coronary heart disease in East and West Finland Scand J clin Lab Invest 1970 25 suppl 113 38

Punsar S & Pyörälä K & Siltanen P Classification of electrocardio-graphic S-T segment changes in epidemiologic studies of coronary heart disease Ann med int Fenn 1968 57 53

Pyörälä K Fyysinen aktiviteetti ja koronaaritauti Duodecim 1972

Nikkilä E A Miettinen T A Vesenne M-R & Pelkonen R Plasma insulin in coronary heart disease Lancet 1965 2 508

Nitter-Hauge & Enge I Relation between blood lipid levels and angiographically evaluated obstructions in coronary arteries Brit Heart J 1973 35 791

Opstad E T Minimal hypertension and insurance mortality - a plea for early treatment Minn Med 1966 49 587

Ostrander Jr L D The relation of silent T wave inversion to cardiovascular disease in an epidemiological study Amer J Cardiol 1970 25 325

Ostrander Jr L D Brandt R L Kjelsberg M O & Epstein F H Electro cardiographic findings among the adult population of a total natural community Tecumseh Michigan Circulation 1965 31 888 (a)

Ostrander Jr L D Francis Jr T Hayner N S Kjelsberg M O & Epstein F H The relationship of cardiovascular disease to hyperglycemia Ann intern Med 1965 62 1188 (b)

Ostrander Jr L D & Weinstein B J Electrocardiographic changes after glucose ingestion Circulation 1964 30 67

Ostrovskaya Tsarfis T P Metelitsa V I & Belokriniskaya L B Disturbed tolerance to carbohydrates as a risk factor in ischaemic disease of the heart according to epidemiological investigation Terapevticeskij archiv 1972 44 57

Paffenbarger Jr R S Prevention of heart disease Postgrad Med 1972 51 74

Palatsi I Feasibility of physical training after myocardial infarction and its effect on return to work morbidity and mortality Academic dis sertation Oulu 1976

Paul O Risks of mild hypertension A ten year report Brit Heart J 1971 33 116

Paul O Lepper M H Phelan W H Dupertuis G W MacMillan A McKean H & Park H A longitudinal study of coronary heart disease Circulation 1963 28 20

Pearson S Stern S & McGavack T H A rapid accurate method for the determination of total cholesterol in serum Anal Chem 1953 25 813

Pell S & D Alonzo C A three year study of myocardial infarction in a large employed population JAMA 1961 175 463

Pesonen E Norio R & Sarna S Thickening in the coronary arteries in infancy as an indication of genetic factors in coronary heart dis ease Circulation 1975 51 218

Punsar S Tupakointi ja sepelvaltimotauti Suom Lääk L 1971 26 27

Punsar S & Karvonen M J Angina pectoris and ECG abnormalities in relation to prognosis of coronary heart disease in population studies in Finland Adv Cardiol 1973 8 148

Punsar S & Pyörälä K Cigarette smoking and the risk of death from coronary heart disease in East and West Finland Scand J clin Lab Invest 1970 25 suppl 113 38

Punsar S & Pyörälä K & Siltanen P Classification of electrocardio-graphic S-T segment changes in epidemiologic studies of coronary heart disease Ann med int Fenn 1968 57 53

Pyörälä K Fyysinen aktiviteetti ja koronaaritauti Duodecim 1972 88 1290

Pyörälä K Sepelvaltimotaudin epidemiologia Suomessa Duodecim 1974 90 1605

Pyörälä K Punsar S Reunanen A Heinonen O P Puro K & Arpomaa A EKG löydökset yhdeksässä suomalaisessa väestöryhmässä Duodecim 1973 89 1299

Pyörälä K Siltanen P Punsar S & Sarna S Riskfaktorer för hjärtinfarkt hos polismän i Helsingfors under 5 års uppföljningsperiod Föredrag i XXXV nordiska kongressen i intern medicin Oulu 1976

Raftery E B Cocker P & Holland W W Value of electrocardiogram in population surveys An attempt to improve interpratation Brit Heart J 1971 33 837

Rauhala V Suomalaisen yhteiskunnan sosiaalinen kerrostuneisuus WSOY Porvoo Helsinki 1966

Reid D D Hamilton P J S McCartney P Rose G Jarrett R J & Keen H Smoking and other risk factors for coronary heart disease in British civil servants Lancet 1976 2 979

Reunanen A Pyörälä K Punsar S Heinonen O P Puro K & Arpomaa A Angina pectoris ja muut rintakivut yhdeksässä suomalaisessa väestö ryhmässä Duodecim 1973 89 668

Rissanen V Aortic and coronary atherosclerosis in a Finnish autopsy series of violent deaths Ann Acad Sci Fenn A V 155 1972

Rodstein M Wolloch L & Gubner R S The significance of minor electro cardiographic T wave changes A mortality study of 518 applicants for insurance Amer J med Sci 1966 252 21

Rose G Detection of high coronary risk Postgrad Med J 1976 52 452

Rose G Variability of angina some implications for epidemiology Brit J prev soc Med 1968 22 12

Rose G Predicting coronary heart disease from minor symptoms and electrocardiographic findings Brit J prev soc Med 1971 25 94

Rose G A & Blackburn H Cardiovascular survey methods World Health Organization monograph series n o 56 Geneva 1968

Roseman R H Friedman M Straus R Jenkins C D Zyzanski S J & Wurm M Coronary heart disease in the western collaborative group study A follow-up experience of 4 5 years J chron Dis 1970 23 173

Roseman R H Friedman M Straus R Wurm M Jenkins C D & Messinger H B Coronary heart disease in the western collaboratory group study A follow-up experience of two years JAMA 1966 195 86

Rotman M Colvard Jr M C Ruskin J & Orgain E S Nonspecific T-wave changes A follow-up study utilizing the T wave screen Arch intern Med 1972 130 895

Royer M E & Howard K O A simplified semiautomated assay for plasma triglycerides Anal Biochem 1969 29 405

Serum cholesterol levels of adults United States 1960-1962 National Center for Health Statistics Series 11 Number 22 1967

Shapiro S Weinblatt E Frank C W & Sager R V Incidence of coronary heart disease in a population insured for medical care Amer J publ Hlth 1969 59 suppl to nr 6

Short D Clinical significance of minor ST/T depression in resting electrocardiogram Brit Heart J 1972 34 377

Short D & Stowers M Earliest symptoms of coronary heart disease and their recognition Brit med J 1972 2 387

Simborg D W The status of risk factors and coronary heart disease J chron Dis 1970 22 515

Simonson E The effect of age on the electrocardiogram Amer J Cardiol 1972 29 64

Sleeper J C & Orgain E S Differentation of benign from pathologic T waves in the electrocardiogram Amer J Cardiol 1963 11 338

Sonquist J A Baker E L & Morgan J N Searching for structure An approach to analysis of substantial bodies of micro-data and documen tation for a computer program Survey Research Center Institute for Social Research The University of Michigan Ann Arbor Michigan 1973

Spain D M & Bradess V A Sudden death from coronary heart disease survival time frequency of thrombi and cigarette smoking Chest 1970 58 107

Stamler J Atherosclerotic coronary heart disease - the major challenge to contemporary public health and preventive medicine Conn Med 1964 28 675

Stamler J Epidemiology of coronary heart disease Med clin N Amer 1973 57 5

Stamler J Lectures on preventive cardiology New York Grune & Stratton 1967

Stamler J Berkson D M & Lindberg H A Risk factors their role in the etiology and pathogenesis of the atherosklerotic diseases In book Pathogenesis of atherosklerosis, edited by R W Wissler & J

Stamler J Berkson D M Lindberg H A Hall Y Miller W Mojonnier L Levinson M Cohen D B & Young Q D Coronary risk factors their impact and their therapy in the prevention of coronary heart disease Med clin N Amer 1966 50 229

Stamler J & Epstein F H Coronary heart disease risk factors as guides to preventive action Prev Med 1972 1 27

Stamler J Lindberg H A Berkson D M Shaffer A Miller W & Poindexter A Prevalence and incidence of coronary heart disease in strata of the labor force of a Chigaco industrial corporation J chron Dis 1960 11 405

Stears S Schlesinger M J & Rudy A Incidence and clinical significance of coronary artery disease in diabetes mellitus Arch intern Med 1947 80 463

Stewart W K & Robertson P C Detection of diabetes mellitus under popu lation survey conditions (Forfar Community Survey 1962) Lancet 1963 2 184

Taylor H L Blackburn H Keys A Parlin R W Vasquez C & Puchner T Coronary heart disease in seven countries IV Five-year follow-up of employees of selected U S railroad companies Circulation 1970 41 suppl I 20

Tibblin G The men born in 1913 study Pehr Dubb J 1969 3 8

Tibblin G & Wilhelmsen L Rökning och koronarsjukdom (5) 1913 års man Läkartidningen 1970 67 153

Weaver J A Bhatis S K Boyle D Hadden D R & Montgomery D A D *Cardio-vascular state of newly discovered diabetic women* Brit med J 1970 1 783

Short D & Stowers M Earliest symptoms of coronary heart disease and their recognition Brit med J 1972 2 387

Simborg D W The status of risk factors and coronary heart disease J chron Dis 1970 22 515

Simonson E The effect of age on the electrocardiogram Amer J Cardiol 1972 29 64

Sleeper J C & Orgain E S Differentation of benign from pathologic T waves in the electrocardiogram Amer J Cardiol 1963 11 338

Sonquist J A Baker E L & Morgan J N Searching for structure An approach to analysis of substantial bodies of micro data and documen tation for a computer program Survey Research Center Institute for Social Research The University of Michigan Ann Arbor Michigan 1973

Spain D M & Bradess V A Sudden death from coronary heart disease survival time frequency of thrombi and cigarette smoking Chest 1970 58 107

Stamler J Atherosclerotic coronary heart disease - the major challenge to contemporary public health and preventive medicine Conn Med 1964 28 675

Stamler J Epidemiology of coronary heart disease Med clin N Amer 1973 57 5

Stamler J Lectures on preventive cardiology New York Grune & Stratton 1967

Stamler J Berkson D M & Lindberg H A Risk factors their role in the etiology and pathogenesis of the atherosklerotic diseases In book Pathogenesis of atherosklerosis edited by R W Wissler & J Geer Baltimore Maryland Williams & Wilkins 1972

Stamler J Berkson D M Lindberg H A Hall Y Miller W Mojonnier L Levinson M Cohen D B & Young Q D Coronary risk factors their impact and their therapy in the prevention of coronary heart disease Med clin N Amer 1966 50 229

Stamler J & Epstein F H Coronary heart disease risk factors as guides to preventive action Prev Med 1972 1 27

Stamler J Lindberg H A Berkson D M Shaffer A Miller W & Poindexter A Prevalence and incidence of coronary heart disease in strata of the labor force of a Chigaco industrial corporation J chron Dis 1960 11 405

Stears S Schlesinger M J & Rudy A Incidence and clinical significance of coronary artery disease in diabetes mellitus Arch intern Med 1947 80 463

Stewart W K & Robertson P C Detection of diabetes mellitus under population survey conditions (Forfar Community Survey 1962) Lancet 1963 2 184

Taylor H L Blackburn H Keys A Parlin R W Vasquez C & Puchner T Coronary heart disease in seven countries IV Five-year follow-up of employees of selected U S railroad companies Circulation 1970 41 suppl I 20

Tibblin G The men born in 1913 study Pehr Dubb J 1969 3:8

Tibblin G & Wilhelmsen L Rökning och koronarsjukdom (5) 1913 års män Läkartidningen 1970 67 153

Weaver J A Bhatis S K Boyle D Hadden D R & Montgomery D A D Cardiovascula state of newly discovered diabetic women Brit med J 1970 1 783

Weinblatt E Shapiro S Frank C W & Sager R W Prognosis of men after first myocardial infarction mortality and first recurrence in relation to selected parameters Amer J publ Hlth 1968 58 1329

Welborn T A Cumpston G N Cullen K J Curnow D H McCall M G & Sten house N S The prevalence of coronary heart disease and associated factors in an Australian rural community Amer J Epid 1969 89 521

Werkö L Risk factors and coronary heart disease facts or fancy? Amer Heart J 1976 91 87

Westlund K & Nicolaysen R Serum cholesterol and risk of mortality and morbidity A 3 year follow up of 6886 men Scand J clin Lab Invest 1966 18 suppl 87

Veterans Administration Cooperative Study Group on Antihypertensive Agents J amer med Ass 1970 213 1143

Wilhelmsen L & Tibblin G Physical activity and risk of myocardial infarction - The men born in 1913 study In book Coronary heart disease and physical fitness Edited by O Andrée Larsen and R O Malmborg Munksgaard Copenhagen 1971

Wilhelmsen L Wedel H & Tibblin G Multivariate analysis of risk factors for coronary heart disease in men aged 50 years in Göteborg Sweden Circulation 1973 48 950

Winsor T The electrocardiogram and coronary insufficiency JAMA 1968 203 97

Woolf C M Principles of biometry Copyright by Van Nostrand Company inc 1968 p 64 (a)

Woolf C M Principles of biometry Copyright by D Van Nostrand Company Inc 1968 p 272 (b)

World Health Organization Cariovascular diseases Annual Statistics 1955-1964 by sex and age Epidem vital Statist Rep 1967 20 539

World Health Organization World Health Statistics Annual 1969 Volume I Vital statistics and causes of death WHO Geneva 1972

Vuopala U Resumption of work after myocardial infarction in Northern Finland Academic dissertation Oulu 1972

Zeiner Henriksen Truls Six year mortality related to cardiorespiratory symptoms and environmental risk factors in a sample of the norwegian population J chron Dis 1976 29 15

Zukel W J Lewis R H Enterline P E Painter R C Ralston L S Fawcett R M Meredith A P & Peterson B A short term community study of the epidemiology of coronary heart disease Amer J publ Hlth 1959 49 1630

Astrand I Areskog N-H Blomquist G Bjerkelund C Carlsten A Furberg C Grewin K E Hansen F Kajser L Kallio V Malmström G Nordgren L Punsar S Pyörälä K & Thuselius O The "Minnesota code for ECG classification Adaptation to CR leads and modification of the code for ECGs recorded during and after exercise Acta med scand 1967 suppl 481

Weinblatt E Shapiro S Frank C W & Sager R W Prognosis of men after first myocardial infarction mortality and first recurrence in relation to selected parameters Amer J publ Hlth 1968 58 1329

Welborn T A Cumpston G N Cullen K J Curnow D H McCall M G & Stenhouse N S The prevalence of coronary heart disease and associated factors in an Australian rural community Amer J Epid 1969 89 521

Werkö L Risk factors and coronary heart disease facts or fancy? Amer Heart J 1976 91 87

Westlund K & Nicolaysen R Serum cholesterol and risk of mortality and morbidity A 3 year follow-up of 6886 men Scand J clin Lab Invest 1966 18 suppl 87

Veterans Administration Cooperative Study Group on Antihypertensive Agents J amer med Ass 1970 213 1143

Wilhelmsen L & Tibblin G Physical activity and risk of myocardial infarction - The men born in 1913 study In book Coronary heart disease and physical fitness Edited by O Andrée Larsen and R O Malmborg Munksgaard Copenhagen 1971

Wilhelmsen L Wedel H & Tibblin G Multivariate analysis of risk factors for coronary heart disease in men aged 50 years in Göteborg Sweden Circulation 1973 48 950

Winsor T The electrocardiogram and coronary insufficiency JAMA 1968 203 97

Woolf C M Principles of biometry Copyright by Van Nostrand Company inc 1968 p 64 (a)

Table 23 Differences of the mean age in the different quintiles Wome

	quintiles		statist difference
Cholesterol	2	4	p< 0 05
	2	5	p< 0 05
Triglyc	1	2	p< 0 05
	1	3	p< 0 05
	1	5	p< 0 01
	4	5	p< 0 05
Syst BP	1	3	p< 0 05
	1	4	p< 0 001
	1	5	p< 0 001
	2	4	p< 0 01
	2	5	p< 0 001
	3	5	p< 0 001
	4	5	p< 0 05
Diast BP	1	4	p< 0 01
	1	5	p< 0 001
	2	3	p< 0 05
	2	4	p 0 001
	2	5	p< 0 001
Blood glucose	1	5	p< 0 01
	2	5	p< 0 01
	4	5	p< 0 01
Weight/height	1	5	p< 0 05
	2	5	p< 0 05
	3	5	p< 0 05
Skinfolds	1	4	p< 0 05
	2	4	p< 0 05

No othe differences between quintiles were found

APPENDIX

Table 22 The mean age in the different quintile Women

Quintile	1	2	3	4	5
Cholesterol	49 3	48 8	50 9	51 3	51 2
Triglyc	48 5	50 7	51 4	49 9	52 0
Syst BP	46 8	47 8	49 6	51 5	53 7
Diast BP	48 2	48 0	51 1	51 9	52 8
Blood glucose	48 6	48 3	50 8	49 7	52 7
Weight/height	49 8	49 1	49 4	51 5	52 1
Skinfolds	48 9	48 9	50 7	52 4	50 6

Table 24 The mean age in the different quintiles Men

Quintile	1	2	3	4	5
Cholesterol	50 7	48 8	50 7	51 0	48 9
Triglyc	49 0	48 4	53 3	49 5	51 1
Syst BP	49 3	50 1	49 6	50 9	50 6
Diast BP	49 9	48 4	52 1	49 9	51 1
Blood glucose	50 6	47 6	49 5	49 6	53 1
Weight/height	49 3	50 6	49 6	49 5	51 1
Skinfolds	48 1	50 6	49 7	51 0	50 8

Table 25 Differences of the mean age in the different quintiles Men

	quintiles	statist difference
Triglyc	1 - 3	$p < 0\ 05$
	2 - 3	$p < 0\ 01$
	3 - 4	$p < 0\ 05$
Dia t BP	2 3	$p = 0\ 05$
Blood gluc	2 5	$p < 0\ 01$
	3 5	$p < 0\ 05$
	4 5	$p < 0\ 05$

No other differences between quintiles were found

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1) Faergeman O & Havel R.J Metabolism of cholesteryl esters f rat very low density lipoproteins Journal f Clinical Investigation 55 1210-1218 1975

2) Mjøs O D Faergeman O Hamilton R.L & Havel R.J Characterization f remnants produced during the metabolism f triglyceride-rich lipoproteins f blood plasma and intestinal lymph in the rat. Journal f Clinical Investi gation 56 603-615 1975

3) Faergeman O Sata T Kane J.P & Havel R.J Metabolism f apoprotein B f plasma very low density lipoproteins in the rat Journal of Clinical Investigation 56 1396-1403 1975

Abbreviations used i this review

apo	poprotein
HDL:	high density lipoproteins
LCAT	lecithin cholesterol acyltransf rase
LDL:	low density lipoproteins
VLDL:	very low den ity lipoproteins

Denne afhandling er i forbindelse med oustående tidligere publicerede afhandlinger af det lægevidenskabelige fakultet ved Københavns Universitet antaget til offentlig at forsvares for den medicinske doktorgrad

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Introduction

The best understood and perhaps most important function f the plasma lipoproteins i transport of triglycerides in chylomicrons very low density lipoproteins (VLDL) from the small intestine or the live to adipose tissue or muscl The l tte ti sues contain in their capillary wall an enzyme lipoprotein lipase that hydrolyses the triglyce ide f chylomicrons and VLDL without removing the whol lipoprotein from th plasma The resulting progressively smalle remnant lipoproteins are ithe removed from plasma in the live or converted to low density lipoproteins (LDL) which in turn may be catabolized in non-hepati tissues High density lipoproteins (HDL) contai littl triglyceride but they do carry proteins serving as cofactors f lipoprotein lipase HDL are lso closely associated with lecithi cholesterol acyltran ferase (LCAT) cholesterol esterifying enzyme f importance i plasma choles rol transport.

The amoun f vailabl information about the plasma lipoprotein system out lined above (Fig 1) i so large that no recent reviews have encompassed it The present one will be no exception Prefaced by bri f discus ion f lipoprotein ructure and synthesi it ill deal mainly with information and ideas about the tabolism f the triglyce ide- ich lipoproteins Pertinent the reviews will be ref rred t frequently

Structure and composition f lipoproteins

Tr glyceride and cholesteryl esters are hydrophobic molecules that can be ansported in the aqueous medium f blood only in combination with more or less hydrophili prot i phospholipid and unesterified cholesterol As in cell mem b anes lipid-protei binding in plasma lipoproteins appears to depend mainly on hydrophobi bonding between phospholipid f tty acid and hydrophobi areas f the prot in (Jackson t l 1976) Chylomicrons and VLDL are large triglyceride-rich lipopro ins with diameters f 750 6 000 Å and 250 750 Å respectively A 2 Å thick monolaye f mainly phospholipid and protein urrounds core f triglyceride

Preface

As will be apparent to the reader Richard J Havel has been important to me The basic studies for this doctoral thesis (Fa rgeman & Havel 1975; Hjøs t al 1975; Faergeman ot al 1975) were performed in 1972 1974 during a research apprenticeship in his laboratory in the Cardiovascular Research Institute University of California San Fr ncisco H was a master teacher and I am very grateful to him Tsunako Sata Agne Frank Leila Kotite Ole D Hjøs Robert L Hamilton John P Kane Chri topher J Fielding Phoebe E Fi lding Philip J Bart r Teizo Sata Philip Frost H John Chapman J tt Fargeman and many others then in San Franci co contributed significantly to these studies with t chnical assistance collaboration advice discussion and agreeabl background noise

In Copenhagen Han Meinertz had i troduced me to the lipoprotein fi ld in 1969 and Anders Tybjærg H nsen has maintained me there I am deeply indebted to them both Other peopl of importance have been and a Jørgen J cobsen Finn Damgaard-Pedersen Johan Georg Kurt Iversen Ulla Vonger J tte Fargeman and many oth rs

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Tabl I Approximate composition f human plasma lipoproteins (weight percent)

Density	HDL 1 063-1 21	LDL 1 006-1 063	VLDL < 1 006	chylomicrons < 1 006
triglyceride	7	8	50	84
cholesteryl ester	15	40	16	4
unesterif chol	3	10	6	2
phospholipid	25	22	18	8
protein	50	20	10	2

hepati and intestinal lipoproteins

The apoproteins i the protein components of lipoproteins have been the obj ct f intense study during the past fifteen years (Shore & Shore 1972; Eisenberg Levy 1975; Jackson et al 1976) Eight apoproteins occurring in normal lipoproteins have been partially cha acterized (Table II) They are identified ither by their carboxy terminal amino acid or by the system f nomenclature proposed by Alaupovic t al (1964) According to the latter the major apoproteins f HDL are designated apo A I and apo A-II the major apoprotein f LDL is apo B and the major apoproteins f VLDL and chylomicrons are apo B and the C I C II and C III apoproteins Thi nomenclature i usually used independently f the unde lying concept f lipoprotein families (Alaupovi 1972) A lipoprotein family" according to Al upovi and his associat and as opposed to the way in which the same term i employed for xampl by Eisenberg & Levy (1975) is system f lipopret ins characterized by the presence f ingl di tinct apolipoprotein or its constitutive polypeptide F r xampl the lipoprotein C family i defined by the presence f apo C it constitutive polypeptides i apo C I apo C II and apo C III Although mai ly present i the very low density range the lipopret i C family xtends into the high density range also

This concept i fundamentally t odds with the generally accepted assumption that the density lasses f lipoproteins separated by ultracentrifugation do approximate physi logically meaningful entities According to the latte concept as it has developed in most f the lipoprotein litterature the apoprotein as well as the lipid components f lipoprot in may be variabl The C group f apoproteins spe ially is known to xchange betwee chylomicrons and VLDL on the one hand and HDL on the other during the process of chylomicron and VLDL catabolism In contrast apo B seems to be an integral component f chylomicrons VLDL and LDL. Apo A I and apo A-II re imilarly integral components f HDL.

Some apoproteins also serve as cofactors fo enzymes active in lipoprotein metabolism The HDL associ ted enzyme LCAT catalyzes the transf f f tty acid from lecithin t cholesterol Apo A-I may participate in the reaction by binding th chol st ryl est product (Fi lding t l 1972) Apo D ("thin line peptide

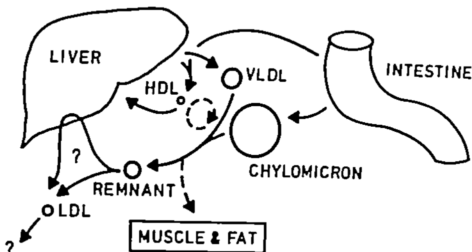


Fig 1 Diagram of the probabl major pathways of plasma lipoprotein metabolism

and some cholesteryl ester (Havel 1975) The surface layer also contains most of the unesterified cholesterol (Zilversmit 1968; Sata et al 1972)

Recent studies suggest the same basic model for the small and denser LDL (diameter 17o - 26o Å) The hydrophobic core of these lipoproteins however is mainly cholesteryl esters (Deckelbaum et al 1975) HDL (diameter 6o 1oo Å) lso have a core of cholesteryl esters The various structural model proposed for HDL differ mainly with respect to the inter relationships of the surface constituents (Jackson et al 1976)

Table I presents approximate average compositional data based on figures in a review by Skipski (1972) Chylomicrons and VLDL vary greatly in size and the tri glyceride content decreases with decreasing particl ize The main phospholipid is lecithi Sphingomyelin and lysol cithin account for significant but smaller proportions Note that the ratio of esterified to unesterified cholesterol increases with increasing lipoprotein density

Chylomicrons and VLDL both carry nough triglyce ide to have dens ties les than 1 oo6 g/ml An etymologically correct definition of chylomicrons as chylous particles of intestinal origin is sometime used to differenti te them from VLDL with a hepatic origin (Hjøe et al 1975) Usually however these lipoprotein classes are defined operationally according to their flotation rate at d 1 o63 in the ana lytical ultracentrifuge Chylomicrons thus have S_f valu gre ter than 4oo and VLDL have S_f values of 2o 4oo In preparative ultracentrifugation $1o^6$ g x min at d 1 oo6 is usually employed to separate chylomicrons from VLDL According to the operational definition which will be used in the following the inte tine produces both chylomicrons and VLDL whereas the liver normally produces only VLDL Thi definition does not preclude important tructural and metabolic diff rences between

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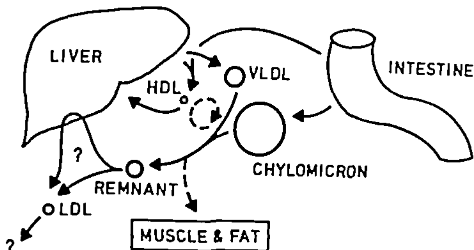


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and VLDL. It has been difficult to study because it tends to aggregate in aqueous medi when delipidated Estimates of molecular weight have ranged from about 255 000 (Smith t al 1972) to about 26,000 (Kane t al 1970) and it may be composed of different subunits Apo B is an essential structural component of chylomicrons VLDL and LDL These lipoproteins are absent from the plasma of patients with abetalipoproteinemi rare disease in which apo B synthesis is defective (Gotto et al 1971) Eisenberg & Levy (1975) suggest that apo B bound to phospholipid and cholesterol constitutes structural nucl us common to chylomicrons VLDL and LDL. Beside this structural rol apo B may interact with the cell surface receptor mediating LDL catabolism to be discussed late If so this interaction is not specifi for apo B ince HDL an abnormal lipoprotein appearing in the plasma of cholesterol fed dogs and swine binds to the recepto although it contains no apo B (Bersot t al 1976)

Synthe i of lipoproteins

Only the liver and small intestine synthesize plasma lipoproteins (Margolis & Capuzzi 1972; Hamilton 1972) During absorption of dietary f t the small intestine secretes large triglyceride-rich lipoproteins (chylomicrons) into the intestinal lymphati vessels In the postabsorptive and fasting states it secretes VLDL whose lipid components come from non-dietary source mainly bile and gastrointestinal mucosal sheddings (Gangl & Ockne 1975) The small intestine thus seems capable f secreting endogenous triglyceride-rich lipoproteins but the liver contri bution to th VLDL pool f plasma is generally thought to be larger The triglyceride incorporated into hepati VLDL are derived mainly from f tty acids extracted from plasma (Havel 1961 Havel t al 1970 (a); Barter t al 1972) but also depending on di t drugs and the state f the live from de novo synthesis of f tty acids from hepati f t stores and from f tty acids originating in the triglyceride f VLDL and chylomicron remnants

The live and small intestine also synthesiz HDL. Studi in rats indicate that both in tinal HDL and triglyceride-rich lipoprot ins are ecreted with apo A-I but without C apoproteins The latte ente the circul tion in hepati HDL and perhaps VLDL (Windmuell al 1973 Herbert et al 1974; Noel & Rubinstein 1974) Some f the HDL gain acces to the intestinal lymph where partial transfe f the C apoproteins t intestinal lipoproteins occurs The imilarity f the metaboli f te f hepati and intestinal triglyceride-rich lipoproteins (Brunzell 1973; Fearyman & Havel 1975; Mjo t l 1975) may largely be due to this transf

Within the cell the apoproteins and lipids f VLDL are synthesized and assembled in ribosomes ttached to the endoplasmi reticulum. The lipoproteins acquire small amount f carbohydrate during the latte part f thei transport through conti uous system f channels f the rough endoplasmi reticulum, the smooth endo-

(...1974; Olofsson & Gustafson 1974) and apo C-I (Garner et al 1972) have also been proposed as LCAT cofactors

Table II   Apoproteins of human plasma lipoproteins

Density	HDL 1 063-1 21	LDL 1 006-1 063	VLDL < 1 006	chylomicrons < 1 006
major apoproteins	A-I A II	B	*A-I B C-I C II C III §E	*A I B C I C II C III E
minor apoproteins	C I C II C III D E			
trace apoproteins	B	C-I C II C III	A-I A-II	A-I A II

*Only in intestinal lipoproteins

§Apo-E arginine-rich apoprotein

The C apoproteins distribute themselves between the triglyceride-rich lipoproteins and HDL according to th conce trations of these lipoproteins in plasma (Eisenberg & Levy 1975) Their tructural functions seem to be unimportant since intestinal VLDL and HDL are secreted without them Apo C II i a cofactor f r *lipoprot in lipase* (Havel et al 197o (b); LaRosa t al 197o) but th possibl metabolic functions of apo C I and C III are not known for certain Although as mentioned above apo C I is on of several candidates for an LCAT cof ctor role it has also been proposed as cofactor for lipoprotein lipase (Wi land et al 1975) Perhaps by way of compens tion for thi uncertainty both apo C I and C III were honored a few years ago by having their amino acid sequence worked out (Brewer t al 1972; Shulman et al 1972)

The arginine-rich apoprotein (Shore t al 1974) r apo E is also a maj r component of normal VLDL (Kane t al 1975) and can be demonstr ted in HDL It is particularly prominent in remnant lipoproteins of th rat (Hjø t al 1975) and in th abnormal beta migrating VLDL of patients with dysbetalipoproteinemia (type III" hyperlipoproteinemia) (H vel & Kane 1973) Since th latter lipoproteins also are thought to be remnants of triglyceride-rich lipoproteins th arginine-rich apoprotein may be intimately involved in remnant metabolism (H vel 1975)

Apo B is the only major apoprotein of LDL and a major apoprotein of chylomicrons

coll agues (Goodman 1965) Redgrave (1970) injected lymph chylomicrons into unanaesthetized rats and found lo minutes l te that the live had removed 83% f the injected cholesteryl ters but only 20% f the injected triglyceride Functional hepatectomy caused accumulation in the plasma of triglyceride-depleted lipoproteins that Redgrave called remnants When remnants were injected into intact rats they were removed very rapidly from the plasma by the liver Bergman t al (1971) measured arterio-venous diff rences across the portal drained viscera the liver and the lower body f sheep and dogs They found that the lowe body selectively removed triglyceride fatty acid f infused lymph chylomicrons but did not measurably take up cholesteryl esters Measurements in the sheep showed that the live and tis was drained by the portal vein accounted fo 85 and 18% f cholesteryl ester removal respectively

The experiments cited above were all conducted with intestinal lipoproteins Mjø t l (1975) tudied formation f remnants from VLDL f blood plasma mainly f hepati rigin as well as from triglyceride-rich lipoproteins f intestinal lymph Es entially imilar results were obtained when the lipoproteins were injected into supradiaphragmati rats anaesthetized animals whose circul tion below the diaphragm had been topped by ligatures around the aorta and the inferior caval and portal vein

Data from one f two imilar experiments re presented in Tabl III Biologically labeled plasma VLDL were obtained from rats injected with (1 2 ^{3}H)cholesterol and (1 ^{14}C)palmitate 6 and 5 hours respectively before bleeding Thirty minutes aft injection into up adiaphragmati ts the rati f recoveries f i jected triglyce ide ^{14}C to est rified chol terol ^{3}H in d < 1 006 lipoproteins had fallen to 25-28 indicating that remnants depl ted f triglyceride relative to cholesteryl est rs had been formed As more triglyceride was removed more esterified cholesterol ^{3}H appeared in the LDL range f d 1 006-1 063 For reasons to be discussed l te the esterified chol terol ^{3}H gradually appearing in d > 1 063 lipopro ins probably represe ted este ification by LCAT f imultaneously injected une rified cholesterol ^{3}H Remnants may thus be formed throughout the whole d < 1 063 pectrum f lipoproteins unde these xperimental conditions The structur l detail f the d < 1 006 part f thi spectrum were tudied more closely P int pe itoneal injection f 4-aminopyrazolopyrimidine which inte alia blocks VLDL ec ion from the live permitted tudy f remnants f chylomicron and VLDL i jected via the aval tump and uncontaminated by the supradiaphragmati animal own VLDL. The remnants appeared by lectron microscopy and chemical compo i on tudi including polyacrylamide gel lectrophoreti separation f apopro i t re ain the fundame tal structure f their precursors A core f cholet ryl t rs and triglyce ide was surrounded by monolaye f unesterified cholerol phospholipid and apoprot ins As triglyceride was removed chol steryl es umed more dominant rol as core mate ial and f the surface compo-nen ph spholipids 1 C nt in seemed to l ave the triglyceride-rich lipo-

plasmic raticulum and the Golgi apparatus (Havel 1975; Eisenberg & Levy 1975) The newly formed VLDL are released from the Golgi apparatus into the space of Disse in the liver or into the lymphatic vessels of th intestine Hepatic VLDL may acquire C apoproteins either immediately prior to this release from the hepatocyte (Hestruck & Rubinstein 1975) or wh n they encounter hepatogenous HDL (Havel 1975)

The intracellular events involved in HDL formation are not as well known HDL may be secreted with an incomplete complement of lipid as discs composed of two layers of apoprotein-phospholipid between which a lipid core of cholesteryl esters is formed in the plasma by LCAT (Forte et al 1974; Hamilton et al 1976)

As will be discussed below LDL are probably catabolic products of the triglyceride-rich lipoproteins and thus may not be independantly secreted from the liver or small intestine

Catabolism of triglyceride-rich lipoproteins

The basis for our current understanding of the c tabolism of the triglyceride-rich lipoproteins was stablished in the 195o (Fredrickson & Gordon 1958) Chylomicrons and VLDL could be shown to be degraded to progressively dense lipoproteins both in vitro wh n they were incubated with po theparin plasma and in vivo after heparin injection Pierce (1954) injected lipoproteins of different densities into rabbits and found by analytical ultracentrifugation that lipoproteins of highe S_f values (chylomicrons and VLDL) were degraded to lipoprot ins of lowe S_f values including th S_f 5 15 class (LDL) and that th reverse proces did not take place Since then a largo number of radioisotope studies of the apoprotein (Gitlin t al 1958; Fidge & Foxman 1971; Bilheimer t al 1972; Eisenberg et al 1973; E enberg & Rachmilewitz 1973; Faergeman et 1 1975; Sigurdsson et al 1975) the triglyceride (H vel t al 1962; Quarfordt et 1 197o; Barte & Ne tel 1972) and the cholesteryl ester components (Lossow et al 1962; Barter 1974; Faergeman & Havel 1975) of chylomicrons or VLDL have confirmed the direction and sequential nature of th process

The remnant hypothesi

Biggs (1957) demonstrated in th rat that triglyceride and cholest ryl esters of chyle lipoproteins were metaboli d differently Wh reas no -h pati tissue removed most of the triglyceride component th liver removed and apparently hydrolyzed th cholesteryl est rs Signif cantly B ggs uggested that the l tt r process occurred last This concept was extended by N tel t al (1963) who found that compl te or partial exclusion of the l ver from th irculation of the dog substantially delayed removal of une terif ed and te ified cholesterol of lymph chylomicrons relative to th triglyceride component The metabolism of the cholesteryl ester component in the rat liver was extens vely tudied by Goodman and his

colleagues (Goodman 1965) Redgrave (197o) injected lymph chylomicrons into unanaesthetized rats and found lo minute later that the liver had removed 83% of the injected cholesteryl esters but only 2o% f the injected triglyceride Functional hepatectomy caused ccumulation in the plasma f triglyceride-depl ted lipoproteins that Redgrave called remnants When remnants were injected into intact rats they were removed very rapidly from the plasma by the liver Bergman et al (1971) measured arterio-venous diff rences across the portal drained viscera the liver and the lowe body f sheep and dogs They found that the lower body selectively removed triglyceride f ty acid f infused lymph chylomicrons but did not measurably take up cholesteryl esters Measurements in the sheep showed that the liver and tissues drained by the portal vein accounted for 85 and 18% f cholesteryl ester removal respectively

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Data from one f two imilar experiment are presented in Tabl III Biologically labeled plasma VLDL were obtained from rats injected with (1 2 ^{3}H)cholesterol and (1 ^{14}C)palmitate 6 and 5 hours respectively before bleeding Thirty minutes ft i jection into supradiaphragmati rats the ti f recoveries f i jected triglyce ide ^{14}C to esterified cholesterol ^{3}H in d < 1 oo6 lipoproteins had fallen to 25-28 indicating that remnants depl ted f triglyceride relative to cholesteryl est rs had been f rmed. As more triglyceride was removed more esterified cholesterol ^{3}H appe red in the LDL range f d 1 oo6-1 o63 For reasons to be discussed l te the te ified cholesterol ^{3}H gradually appearing in d > 1 o63 lipoprot ins probably represented este ification by LCAT f imultaneously injected unest ified cholest rol ^{3}H Remnants may thus be formed throughout the whol d 1 o63 pectrum f lipoproteins unde these xperimental condition The structur l detail f the d < 1 oo6 part f this spectrum were studied more closely P i i tr pe itoneal injection f 4-aminopyrazolepyrimidine which inte lia block VLDL sec etion from the live permitted tudy f remnants f chylomicrons and VLDL injected vi the val ump and uncontaminated by the supradiaphragmati animal own VLDL. The remnants appeared by lectron microscopy and chemical compo i ion udi including polyacrylamide gel lectrophoreti separation f apopro i retain the fundamental structure f their precursors A core f cholesryl and triglyce ide as surrounded by monolaye f une terified cholerol phospholipid and poprot ins As triglyceride was removed cholesteryl umed mo dmina rel as core mate ial and f the surface component phospholipids and C aoprot in seemed to l ave the triglyceride-rich lipo-

plasmic reticulum and the Golgi apparatus (Havel 1975; Eisenberg & Levy 1975) Th newly formed VLDL are released from the Golgi apparatus into the space of Disse i the liver or into the lymphatic vessels of the inte tine H patic VLDL may acquir C apoproteins either immediately prior to this release from the hepatocyte (Hes-truck & Rubinstein 1975) or when they encounter hepatogenous HDL (Havel 1975)

The intracellular events involved in HDL formation are not as well known HDL may be secreted with an incomplete complement of lipid as discs composed of two layers of apoprotein-phospholipid between which a lipid core of cholesteryl este is formed in the plasma by LCAT (Forte et al 1974; Hamilton t al 1976)

As will be discussed below LDL re probably cataboli products of the triglyce-ride-rich lipoproteins and thus may not be independently secreted from th liver or small intestine

Catabolism of triglyceride-rich lipoproteins

The basis for our current understanding of the catabolism of the triglyceride-rich lipoprotein was established in the 195o s (Fredrickson & Gordon 1958) Chylo-microns and VLDL could be shown to be degraded to progressively denser l poprotein both in vitro when they were incubated with postheparin plasma and in vivo after heparin injection Pierce (1954) injected lipoprotein of diff rent den ities into rabbits and found by analytical ultracentrifugation that lipoproteins f higher S_f values (chylomicrons and VLDL) were degraded to lipoproteins of lowe S_f values including th S_f 5 15 class (LDL) and that the reverse process did not take place Since then a large number of radioisotope tudies of the apoprotein (Gitlin t al 1958; Fidge & Poxman 1971; B lheimer et al 1972; Eisenberg t al 1973; Eisen-berg & Rachmilewitz 1973; Faergeman t al 197 ; Sigurdsson t al 1975) the triglyceride (Havel et al 1962; Qua fordt t al 197o; Barter & Ne tel 1972) and the cholesteryl ester components (Lossow et al 1962; Barter 1974; Faergeman & Havel 1975) of chylomicrons or VLDL have confirmed the direction and sequential nature of th process

The remnant hypothesis

Biggs (1957) demonstrated in th rat that triglyceride and cholesteryl sters of chyl lipoproteins were metabolized differently Wh reas non-h pati tis ues removed most of th triglyceride component the liver removed and appare tly hydro-lyzed th cholesteryl esters Significantly Biggs uggested that th latter pro-cess occurred last This concept was extended by N tel t al (1963) who found that compl te or partial exclusion of the liver from th irculation of the dog substantially delayed removal of unesterif ed and esterified cholesterol of lymph chylomicrons relative to the triglyceride component The metabolism of th chole-steryl ester component in the rat l ver was extensively studied by Goodman and his

colleagues (Goodman 1965) Redgrave (1970) injected lymph chylomicrons into unanesthetized rats and found 10 minutes later that the liver had removed 83% of the injected cholesteryl esters but only 20% f the injected triglyceride Functional hepatectomy caused accumulation in the plasma f triglyceride-depleted lipoproteins that Redgrave called remnants When remnants were injected into intact rats they were removed very rapidly from the plasma by the liver Bergman t al (1971) measured arterio-venous differences across the portal drained viscera the live and the lower body f sheep and dogs They found that the lower body selectively removed triglyceride f tty acid f infused lymph chylomicrons but did not measurably take up cholesteryl esters Measurements in the sheep showed that the liver and tissues drained by the portal vein accounted for 85 and 10% of cholesteryl este removal respectively

The experiments cited above were all conducted with intestinal lipoproteins Mjø t al (1975) studied formation f remnants from VLDL f blood plasma mainly of hepati origin as well as from triglyceride-rich lipoproteins f int stinal lymph Essentially similar results were obtained when the lipoproteins were injected into supradiaphragmati rats anesthetized animals whose irculation below the diaphragm had been topped by ligatures around the aorta and the inferior caval and portal veins

Data from one f two similar experiments are presented in Tabl III Biologically labeled plasma VLDL were obtained from rats injected with (1 2 ^{3}H)cholesterol and (1 ^{14}C)palmitate 6 and .5 hours respectively before bleeding Thirty minutes after injection into upradiaphragmati rats the ratio of recoveries f injected triglyceride ^{14}C to esterified cholesterol ^{3}H in d < 1 006 lipoproteins had fallen to 25-28% indicating that remnants depleted f triglyceride relative to cholesteryl esters had been formed As more triglyceride was removed more esterified cholesterol ^{3} appeared in the LDL range f d 1 006-1.063 For reasons to be discussed l te the esterified cholesterol ^{3}H gradually appearing in d > 1.063 lipoproteins probably represented esterification by LCAT f simultaneously injected unesterified cholesterol ^{3}H Remnants may thus be formed throughout the whole d < 1 063 spectrum f lipoproteins under these experimental conditions The structural details f the d 1 006 part f this spectrum were studied more losely Prior intraperitoneal injection f 4-aminopyrazolepyrimidine which inte alia blocks VLDL secretion from the liver permitted study f remnants of chylomicrons and VLDL injected via the caval tump and uncontaminated by the supradiaphragmati animal own VLDL The remnants appeared by lectron microscopy and chemical composi ion studies including polyacrylamide gel l ctrophoreti separation f apoprotein to retain the fundamental structure f their precursors A core of cholesteryl esters and triglycerides was surrounded by monolayer f unesterified cholesterol phospholipid and apoproteins As triglyceride was removed cholesteryl este assumed more dominant rol as core material and, f the surface components phospholipids and C apoproteins seemed to leave the triglyceride-rich lipo-

Tabl III Distribution of Radioactivity in Lipids of Lipoprotein Fractions after Injection of Doubly Labeled VLDL into Supradiaphragmatic Rats

Time after injection	Esterified ^{3}H cholesterol as percent of that injected*					Injected ^{14}C recovered in		
	d < 1 oo6	d 1 oo6–1 o19	d 1 o19 1 o63	Total in d < 1 o63	Total in d > 1 o63	d < 1 oo6 TGFA	d > 1 o63 FFA	Recovery ratio$
min	%					%		
2 5	66 9	4 2	1 2	72 3	1 6	62 8	3 o	o 94
2 5	64 3	4 9	3 7	72 9	2 2	37 6	18 6	o 58
5	78 5	2 o	1 4	81 9	2 9	6o 7	8 8	o 77
5	61 4	5 1	5 1	71 6	2 7	29 2	1o 3	o 48
15	63 o	7 4	1o 2	8o 6	3 7	26 6	6 2	o 42
15	33 6	14 o	27 7	75 3	4 5	4 4	1 4	o 13
3o	53 7	8 6	11 2	73 5	5 5	13 2	o 8	o 25
3o	64 3	5 8	5 4	75 5	6 6	17 7	1 1	o 28

*Calculated from radioactivity contained in blood plasma Plasma volume was det rmined for each rat from dilution of ^{125}I labeled human serum albumin

$Ratio of ^{14}C triglyceride fatty acid to esterified ^{3}H chol sterol in d < 1 oo6 lipoproteins (ratio in injected material normalized to unity)

TGFA triglyceride fatty acid FFA free fatty acids

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proteins Whereas apoproteins identified as the arginine-rich peptide and in the case f intestinal lipoproteins apo A-I seemed to remain apo B could in the case f VLDL remnants be shown to be the most constant component

These rat studies suggested that hepati and intestinal triglyceride-rich lipoproteins are catabolized by similar if not identical mechanisms as far as the lipoprotein lipase step Similar conclusions were drawn by Brunzell t al (1973) on the basis of human studies On the ther hand Wieland et al (1975) have presented preliminary vidence that human intestinal and hepati triglyceride-rich lipoproteins are catabolized by different apo C I and apo C II activated lipoprotein lipases respectively

In the supradiaphragmatic rat the lipoprotein lipase( ) f adipose tissue skelet al muscle and heart may complete the conversion f triglyceride-rich lipoproteins to LDL (Table III) Isolated rat heart studies have shown that as triglyceride is removed, the remnant lipoproteins become progressively poorer substrate for lipoprotein lipase (Fielding & Higgins 1974) possibly due to the concomitant loss of the lipoprotein lipase cofacto apo C II demonstrated in studies f VLDL incubated with post-heparin plasma (Eisenberg & Rachmilewitz 1975) In the intact animal remnant lipoproteins are vulnerabl to removal by the liver before serial passages through extra-hepati tissues allow lipoprotein lipase to degrade them completely to LDL. The extent f this degradation may be complex function f lipoprotein structure lipoprotein interactions lipoprotein lipase fficiency remnant affinity for liver cell and possibly ther metabolic parameters Not surprisingly therefore i varies importantly between animal species as will appear later In the following the fate of the various components f chylomicrons and VLDL will be considered, with emphasis on cholesteryl esters and apo B

Phospholipids and unesterified cholesterol Rubenstein Rubinstein (1972) found that lecithin and sphingomyelin f rat VLDL transferred mainly to HDL both in vivo and in vitro Small amounts f both phospholipids but relatively more sphingomyelin were also recovered in LDL. Whereas C apoproteins in the same experiments apparently exchanged between VLDL and HDL the phospholipids seemed to transfer unidirectionally Thi may be due t least in part to the action f LCAT (Norum 1971 Glomset 1972) Located on HDL this enzyme catalyzes the transfer of an acyl group from the 2 position of lecithin to the 3 position of cholesterol Whereas the resulting lysolecithin becomes associated with $d > 1.21$ proteins f plasma the esterified cholesterol esters the putative core of the HDL particle (Faergeman & Havel 1975) By favouring net transfer f both surface constituents lecithin and cholesterol from the triglyceride-rich lipoproteins to HDL LCAT acts to reduce surface material as core triglyceride is removed by lipoprotein lipase (Schumaker Adams 1970) The basic tructure f the triglyceride-rich lipoproteins is therefore retained in their remnants (Mjøs et al 1975) Recent in vitro studies suggest that the phospholipase activity associated with lipoprotein lipase and hepati triglyce-

ride hydrolase may be as important as LCAT in removing phospholipids from triglyceride-rich *lipoproteins* (*Eisenberg & Schurr 1976*) In the intact animal molecular exchange of phospholipids and unesterified cholesterol between triglyceride-rich lipoproteins and various cell membranes may interact significantly with these enzymatic processes

C apoproteins   Several groups of investigators have demonstrated the ready exchange of C apoproteins between triglyceride-rich lipoproteins and HDL (Eisenberg & Levy 1975; Rubenstein & Rubinstein 1972; *Havel et al 1973; Faergeman et al 1975*) In association with the relatively slowly turning over pool of HDL the C apoproteins *constitute a circulating* supply of cofactors readily vailabl to the fluctuating requirements of triglyceride-rich lipoprotein catabolism.

Triglyceride   After hydrolysis of the ester bond by lipoprotein lipase in adipose tissue skeletal muscle or heart (Olivecrona & Belfrage 1965; Havel 1965; Nikkilä 1969) the fatty acids are either taken up by the parenchymal cells or as illustrated in Table III released into the blood tream where they attach to albumin for rapid transit to other tissue including the liver Whereas extra-hepatic tissues remove only small amounts of the other lipid constituents of chylomicrons and VLDL hepatic uptake of triglyceride fatty acids probably occurs as part of hepatic remnant removal (H vel 1965; Elovson t l 1965; Belf ge 1968) Between 10 and 30% *of chylomicron and VLDL triglyceride* may reach the liver but thi varies between animal species and depends on the nutritional tate of the animal (*Havel et al 1962; Havel 1965; Bergman t al 1971; Fa rgeman & Havel 1975*; Nilsson Ehle 1975) An undetermined amount of chylomicron or VLDL triglyceride may transfer to a r pidly turning ove HDL subf ction (Barter & Connor *1975*) whose ultimate fate is uncertain

Injection of heparin causes th release into plasma of both lipoprotei lipase and a hepatic triglyceride hydrolase Despite speculation about pos ibl rol in hydrolyzing residual triglyceride and phospholipid in remnant lipoproteins (Eisenberg & Levy 1975) the function of th hepatic enzyme i unknown Its contribution to po t heparin lipase ctivity of human plasma increased by treatment with oxandrolone a synthetic steroid (Ehnholm t al 1975) This may explain the poor correlation betwee triglyceride emoval eff ciency and total post heparin lipase activity obe rved in oxandrolone treated pati ts with exogenous (Fa rgeman & Damgaard-Pedersen 1973) and endogenous hypertr glycer demia (Glueck t al 1973)

Chole terol   Discussion of the metabolism *of* un terif ed and espe ially the esterified cholesterol of chylomicrons and VLDL require consideration of th *sources of plasma* cholesteryl esters and th ir transf r between lipoprot ins The mucosal cells of the small int tine contain enzymes capabl f t ifying the

major part of absorbed dietary cholesterol before its incorporation into VLDL and chylomicrons (Goodman 1965; Zndel et al 1973) The source f cholesteryl esters in VLDL of hepati rigin however may vary between species Rat VLDL derive their cholesteryl esters mainly from hepati cholesterol esterifying enzyme (f tty acyl coA cholesterol acyltransferase) (Goodman 1965) located in the Golgi ppa-ratus where VLDL formation is completed (Assmann et al 1974) Rabbit VLDL may also especially during cholesterol feeding derive most f their cholesteryl esters from the liver (Rose 1972) Cholesterol esterifying enzymes are apparently not present in human live howeve (Stokke 1972) and cholesteryl esters of human plasma not derived from the intestine have ll been thought to be formed in plasma by LCAT (Glomset 1972) The question f possible hepati contribution to cholest ryl esters f human plasma is nevertheless till open (Barte 1974)

In contrast to the case in the human the composition f rat plasma cholesteryl esters varies between lipoprotein classes (Gidez t al 1965; Faergeman & Havel 1975) Whereas HDL cholesterol is esterified mainly with 2o 4 and 18 2 f tty acids reflecting LCAT mediated transf from lecithin VLDL cholesteryl stars contain mostly 18 1 18 2 and 16 acids reflecting hepati rigin (Gidez t 1 1967) LDL cholesteryl ester composition is intermediate This heterogeneity facilitated studie f transport in plasma f rat cholesteryl esters (Faergeman & Havel 1975)

As in remnant studies previous studi f cholesteryl este metabolism in tri glyceride-rich lipoproteins had been performed with intestinal lipoproteins (Good-man 1962 Quarfordt & Goodman 1967 Quarfordt Goodman 1969 Stein et al 1969) Faergeman Havel (1975) obtained biologically labeled plasma VLDL from rats in-jected 6 hours previously with ^{3} -cholesterol About 3o% f the labeled cholesterol was in sterified form When injected into recipient rats most of the esterified and unesterified cholesterol ^{3}H was rapidly taken up in the liver where the chole-steryl esters subsequently were hydrolyzed (Tables IV and V) A small fraction f the injected esterified cholesterol ^{3}H about 3% ppeared via lipoproteins of intermediat density (d 1 oo6-1 19) in LDL (d 1 o19-1.o63) f plasma Argentation thin layer chromatography studie showed that the di tribution f cholesterol ^{3}H in the various ters f LDL and the live was the same as that of the injected VLDL. I contrast distribution f cholesterol ^{3}H gradually ppea ing in HDL re-flected esterification by LCAT f the imultaneously injected unesterified chole-terol ^{3}H Since the mass distribution f cholesteryl esters in LDL as determined by gas liquid chromatography was intermediate between that f VLDL and HDL it was apparen that LDL esters had dual origin transfer from VLDL and LCAT esteri fication presumably on HDL with ubsequen transf to LDL.

The extensive hepati removal from plasma f both cholesteryl esters co component and unesterified cholesterol surface component suggested endocytosis f the whol VLDL remnant Early experiments in these studies showed that small tructural change in the injected VLDL could markedly affect this hepatic uptake mechanism. As in Goodman (1962) work with chylomicrons the ratio f esterified

Table IV   Esterifi d ^{3}H-Cholesterol as Percentage of Injected VLDL Esterifi d ^{3}H-Cholesterol

Time after inj ction	Plasma lipoproteins				
	d < 1 oo6 (n = 8)	d 1 oo6-1 o19 (n = 8)	d 1 o19 1 o63 (n = 8)	d > 1 o63 (n = 6)	Liver (n = 8)
min					
5	37 9 (12 3)*	2 2 (1 1)	1 2 (o 7)	1 3 (o 3)	5o 8 (12 9)
1o	2o 2§	1 9	1 5	1 5	64 5
15	8 8 (6 8)	2 5 (1 3)	1 6 (1 2)	1 4 (o 3)	7o 9 (1o 2)
3o	1 5 (o 9)	2 1 (1 6)	2 3 (1 7)	1 7 (o 5)	31 2 (8 8)
6o	1 6 (o 5)	1 4 (o 9)	3 3 (1 8)	3 2 (1 2)	12 4 (2 4)

Mean and SD values calculated for plasma volume = 4% of body wt

§ n 2

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Tabl V Free ^{3}H-Cholesterol as Percent f Injected VLDL Free ^{3}H-Cholesterol

Time after injection	Plasma lipoproteins				Live
	d < 1 006 (8)	d 1 006-1 019 (n 8)	d 1 19-1 063 (8)	d > 1 063 (6)	(8)
min					
5	26 7 (1 7)	1 4 (8)	4 1 (1 1)	6 9 (8)	53 5 (7 5)
10	13 7§	1 1	3 4	4 9	59 9
15	4 4 (3 8)	9 (5)	1 9 (5)	2 9 (8)	74 2 (9 9)
30	9 (4)	6 (4)	1 6 (4)	2 3 (3)	91 9 (14)
60	1 5 (6)	6 (4)	1 8 (7)	3 3 (4)	82 (8 3)

Mean and SD values calculated for plasma volume 4% f body wt

§ 2

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Table IV Esterified ^{3}H-Cholesterol as Percentage of Inj cted VLDL Esterifi d ^{3}H-Cholesterol

Time after injection	Plasma lipoproteins				
	d < 1 oo6 (n = 8)	d 1 oo6–1 o19 (n = 8)	d 1 o19–1 o63 (n = 8)	d > 1 o63 (n = 6)	Liver (n = 8)
min					
5	37 9 (12 3)*	2 2 (1 1)	1 2 (o 7)	1 3 (o 3)	5o 8 (12 9)
1o	2o 2$	1 9	1 5	1 5	64 5
15	8 8 (6 8)	2 5 (1 3)	1 6 (1 2)	1 4 (o 3)	7o 9 (1o 2)
3o	1 5 (o 9)	2 1 (1 6)	2 3 (1 7)	1 7 (o 5)	31 2 (8 8)
6o	1 6 (o 5)	1 4 (o 9)	3 3 (1 8)	3 2 (1 2)	12 4 (2 4)

*Mean and SD values alculated for plasma volume = 4% of body wt

$ = 2

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The possibl importance f cholesteryl este transf reactions fo transport of cholesterol from non-hepatic tissues to the live will be considered t the end of this review

B apoprotein The heterogeneous origin f the cholesteryl esters of rat LDL contrasts with the finding that the ther major LDL component apo B is probably exclusively derived from VLDL (Faergeman et al 1975) These studies were also based on work with biologically labeled VLDL The incorporation of intravenously injected ^{3}H lysine into tetramethylurea insolubl (apo B) and soluble (mainly apo C) apoproteins f VLDL and LDL produced specific activity curve compatible with precursor-product relationship between apo B of VLDL and LDL respectively (Fig 2) When VLDL labeled in this manner were injected into othe rats the f te of apo B closely approximated that f cholesteryl esters small amount about 3% was recovered in plasma LDL whereas the major part rapidly ppeared in the live where it was lowly degraded (Tabl VI) In these recipient rats the specific activity relationships again indicated that apo B f VLDL could be the sol precurso f LDL apo B Incubation f labeled VLDL with unlabeled HDL decreased the amount f ^{3}H due to non B apoproteins (C apoproteins) from about 35 to 14% by molecular exchange This incubation procedure did not as had been the case with erythrocyte incubation affect the metabolic behaviour f the VLDL in ecipien rats

These studies were in essential agreement with tudies f ^{125}I labeled VLDL also conducted in the rat (Eisenberg & Rachmilewitz 1973; Bobeis t al 1973) and supported the usefulness f the latte more extensively employed techniques in metabolic experiments f this kind (Fidge Poulis 1974) Moreove they were the first along with imultaneously published studies f human lipoproteins (Sigurdsson t al 1975 Phair al 1975) to document with specifi activity data the concept f precursor-product relationship between apo B f VLDL and LDL Both human and rat LDL thus seem to originate in plasma VLDL. Howeve the extent to which VLDL apo B is converted to LDL apo B or rapidly removed in the live differs markedly in these two specie as will be discussed below

Remnan uptake in the live

The perfused rat live can remove from the perfusate in vitro labeled cholesteryl esters f intact inte tinal chylomicrons (Quarfordt D.S Goodman 1969) or intact serum lipoproteins (Z D Goodman LeQuire 1975) and the latter authors suggested tha xchange f cholesteryl este between lipoproteins and hepatocytes is physiologically importan Howeve the rate f uptak and subsequent hydrolysis is faste when the perfused live is presented with lipoproteins that have passed through nonhepati tissue (Quarfordt & D S Goodman 1969; Sherrill & Dietschy 1976) This trengthens the impression gained from studie with intact animals that hepati removal f VLDL or chylomicron components occurs during uptake of intact remnant

to unesterified chol terol ^{3}H in donor VLDL could be increased substantially by incubation of the lipoproteins with erythrocytes containing exchangeable unlabeled unesterified cholesterol Th chol sterol ^{3}H of the incubated VLDL however appeared in the liver of recipient animals much more rapidly than that of unincubated VLDL and more extensive hepatic uptake of ^{14}C triglyceride fatty acid occurred Incubated VLDL contained more unesterifi d cholesterol and less phospholipid than the unincubated lipoproteins Small alterations of these surface components may thus dramatically affect the manner in which the lipoprotein is metabolized

These cholesteryl ter tudies indicated that a in the case of chylomicrons the remnants of rat VLDL are rapidly taken up in th liver and that *only a minor* part complete the conversion to LDL Moreover they showed that rat LDL cholesteryl *esters are apparently derived from* both VLDL and HDL associated LCAT Glomset (1972) has suggested that chol teryl e ters of HDL *may be transferred to the triglyceride*-rich lipoproteins in exchange for lecithin unesterifi d cholesterol and a small amount of triglyceride The mechanism of this transfer has been th subject f different incubation studies In a preliminary report Glomset t al (1974) proposed that LCAT mediates transfer of the arginine-rich poprotein from HDL to VLDL in conjunction with cholesteryl esters Thi agrees well with findings that the arginine-rich apoprotein is prominent in rat VLDL and chylomicron remnants (Hjøs et al 1975) and in human dysbetalipoproteinemia (Havel & Kane 1973)

Recently Olofsson (1975) found that incubation of a HDL subfraction obtained by hydroxyl apatite column chromatography brok up the lipoprotein in a lipid poor fraction ("HDL^{inf}) and a fraction ("HDL^{sup}) composed mainly of cholesteryl esters coupled to a polypeptide different from th recognized apoproteins of HDL Th author suggested that this polypeptide transf rs chole teryl esters from HDL to VLDL in vivo Whether HDL subfractions isolated by in vitro technique of thi kind may correspond to th *rapidly turning over HDL* ubpool uggested by in vivo studi s (Barter 1974; Barter & Connor 1975; Barter t al 1977) is unknown

The concept of cholesteryl ester acquisition by triglyceride-r ch lipoproteins and their remnants is not readily consistent with all vailabl data howeve Using calculations based on median molecul we ghts of subfractions of the S_f *20-400 range Eisenberg t al (1973) found in a* tudy f hyperlip demi humans that in one ubject the esterified chole terol content of each particl decreased with increasing particl density In anoth subj ct *it remained constant Similar*ly Eisenberg & Rachmilewitz (1975) calculated that in vitro conversion of rat VLDL to remnants by postheparin plasma involved loss of all components except po B In contrast Hjøs t al (1975) employing calcul tions based on molecular weights derived from chemical composition tudies nd lectron microscopi determination f particle izes found that th cholesteryl ester cont nt pe particl increased as VLDL were degraded to remnants This increase seems to depend on the vailab lity *of HDL* ince it did not occur in 4 aminopyrazolepy imidin treated rats in wh ch HDL l vels were low

The possibl importance f cholesteryl este transfer reactions fo transport f holesterol from non-hepatic tissues to the live will be considered t the end f his review

apoproteins The heterogenous rigin f the cholesteryl esters f rat LDL contrasts with the finding that the othe majo LDL component apo B is probably xclusively derived from VLDL (Faergeman t al 1975) These studie were also ased on work with biologically labeled VLDL The incorporation f intravenously njected ^{3}H-lysine into tetramethylurea insolubl (apo B) and solubl (mainly apo C) apoproteins f VLDL and LDL produced specific activity curves compatible with precurso -product relationship between apo B of VLDL and LDL respectively (Fig 2) When VLDL labeled in this manner were injected into othe rats the fate f apo B closely approximated that f cholesteryl esters small amount about 3% was recovered in plasma LDL whereas the major part rapidly ppeared in the liver where it was lowly degraded (Tabl VI) In these recipient rats the pecifi activity relationships again indicated that po B f VLDL could be the sol precursor f LDL po B Incubation f labeled VLDL with unlabeled HDL decreased the amount f ^{3}H due to non B apoproteins (C poproteins) from about 35 to 14% by molecular exchange This incubation procedure did not as had been the case with erythrocyte incubation affect the metabolic behaviour of the VLDL in recipient rats These tudies were in essential agreement with studies f ^{125}I labeled VLDL also conducted in the rat (Eisenberg Rachmilevitz 1973 Roheim t al 1973) and supported the usefulness f the latte more extensively employed techniques in meta bolic experiments f this kind (Ridge & Poulis 1974) Moreove they were the first along with simultaneously published tudies f human lipoproteins (Sigurdsson et al 1975 Phair t al 1975) to document with specific activity data the concept f precurso product rel tionship between apo B f VLDL and LDL. Both human and rat LDL thus seem to riginate in plasma VLDL. However the extent to which VLDL apo i converted to LDL apo B or rapidly removed in the live differs markedly in these two specie as will be discussed below

Remnant uptake in the liver

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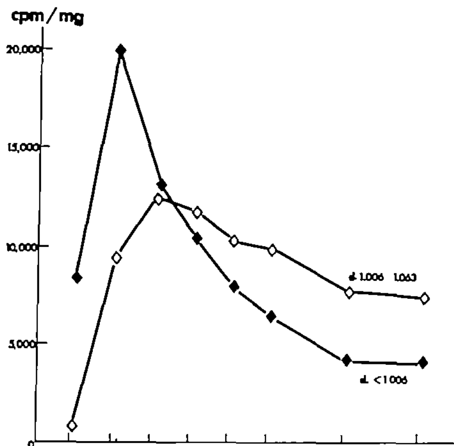


Fig 2 Specific activity of tetramethylurea insoluble apoprotein (po B) of VLDL and LDL of ^{3}H lysine injected rats Each point represents pooled lipoprotein from 3 animals (Reproduced with permission of J clin Invest)

lipoproteins (Belfrage 1968; Havel 1965; Bergman et al 1971; Stein t al 1969; Faergeman & Havel 1975; Stein et al 1974; Faergeman t al 1975) For example cholesteryl esters and apo B components of VLDL are taken up in the liver to similar extent and at similar rate consistent with uptake of both components in one unit (Faergeman & Havel 1975; Faergeman et al 1975)

Whereas the triglycerides may be hydrolyzed whil th remnant is attached to the hepatocyte plasma membrane (Belfrage 1968) the apoprotein may be degraded in secondary lysosomes of the cell interior (Stein et al 1974) Hydrolysis of cholesteryl stars seems to occur at or immediately inside the plasma membrane (Stein et al 1969) possibly in secondary lysosomes (Stein t al 1977)

Control of remnant uptake in th liver is the obj ct f considerabl interest Although subtle alterations in the unesterified chol sterol and phospholipid surface components of th VLDL precursor may affect the rate of uptake (Fa rgeman & Havel 1975) a characteristic component of remnants would seem more lik ly to trigger recognition by the liver Havel (1975) ha suggested that th arginine-rich apoprotein may serve this purpose After remnant uptake in the liver the arginine-rich apoprotein may recycl into the plasma to become associ ted with HDL

Tabl VI Dist ibution f ^{3}H afte Intr venous Injection f ^{3}H-Lysine-Labeled VLDL Incubated with HDL to Bedvos ^{3}H in TMU-Solubl Proteins

	Numbe f rats	Time afte injection: 5 min	15 min	30 min	60 min
		% f injected ^{3}H			
Lipoproteins					
d < 1 006	8	32 7 13 4‡	12 8 + 6 8	7 1 + 3 5	2 4 + 1 2
	(4)§	(34 3 14 4)	(11 9 7 7)	(4 9 2 3)	(1 + 1)
d 1 006-1 19	8	2 1 1 1	2 4 1 3	2 o + 8	1 o 5
d 1 19-1 063	8	8 3	2 o + 7	2 6 7	2 9 + 9
	(4)	(6 3)	(1 7 8)	(2 4 + 8)	(2 7 + 1)
d 1 063-1 21	8	3 8 1 8	4 1 2	2 9 1 8	4 1 2 4
d > 1 21	6	1 9 1 4	2 3 + 1 2	1 9 + 1 5	4 + 2 4
Organs					
Liver	8	36 3 11 5	5o 5 5 3	48 5 8 3	4o 9 + 1o 4
Intestine	4	4 1	8 + 6	1 8 1 7	1 o 1 o
Spleen	2		4		o 3
Kidneys	2		1		1
Heart	2		3		o 2
Lungs	2		8		1 6
Total		78	77 5	66 8	59 4

*Based upon plasma volume f 4 5% f body weight

‡Mean values SD

§Numbers in parenthesis refe to TMU-insolubl protein as percent f inj cted TMU-insoluble ^{3}H 86% f the labeled protein injected was insolubl in TMU

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and d > 1 21 proteins The hepatocyte surface may possess a remnant specific receptor since evidence presented in abstract form by Sherrill & Dietschy (1976) sugge that remnant uptake in the liver is a specific saturabl process

Transfer of apo B from VLDL to LDL

The appearance of a small amount of radioactivity in LDL prot in after ^{14}C leucine injection into squirrel monkeys whose VLDL catabolism had been blocked by Triton treatment suggested (Illingworth 1975) that a small amount of LDL apo B in this species may not be derived from VLDL However the pr viously mentioned specific activity data obtained in the rat (Faergeman et al 197) and human (Sigurdsson et al 1975) are consistent with the general impression that all LDL apo B is derived from VLDL apo B

On the oth r hand the extent to which VLDL ar convert d to LDL varies importantly between species In the rat the amount of injected VLDL apo B that can be recovered in LDL is substantially less than 10% (Eis nberg & Rachmilewitz 1973; Faergeman et al 1975) This is consi tent with a c lculation showing th LDL apo B turnover rate (mass/time) to be about 4% of that of VLDL apo B (Faergeman t al 1975) Essentially the same conclusion could be drawn from studi s of the metabolism of the cholest ryl ester component of rat VLDL (Faergeman & Havel 1)7) VLDL metabolism in the human is very diff rent Recovery in plasma LDL of simultaneously inj cted ^{131}I VLDL apo B and ^{125}I LDL apo B into normal human su j cts allowed Sigurdsson t al (1975) to calcul t by two diff r nt techniques t t a mean of about 90% of VLDL apo B was converted to LDL po B In separat experiments these authors found that the mean turnover rat of po B in LDL was about 82% of that of VLDL apo B with substantial variation They concluded t t most if not all human VLDL apo B is converted to LDL po B

Exactly how uptak of remnants in th liver i r l ted to LDL formation is unknown (Fig 1) One possibility is uptak of all remnant in the liver removal of most of the residual triglyc ride and non B apoprot ins and rel as into plasma of the resulting LDL in an amount variabl between animal spe i (Havel 197) Anoth r possibility mentioned pr viously i upt ke i the liver of riabl proportion of the remnants produced by lipoprotei lipase whic compl tes th conversion to LDL of remnants scaping th liver I th l tte case the liver is not directly involved in LDL formation Whatever the meche ism the xt t of LDL formation from VLDL may determine speci charact ri ti plasma LDL trations In the human most of VLDL i converted to LDL and LDL l vel r high The opposite is true in the rat and th guin pig is intermedi t i his spect (Barter et al 1977)

Catabolism of LDL

Recent tudi f cell cultures and in intact animals suggest that LDL are cata bolized in non-hepati tissues The molecular basis fo this process has been studied in several laboratorie notably that f Brown Goldstein and their co-workers (Brown & Goldstein 1976) Results f experiments with culture f fibroblasts from normal humans and patients with familial hypercholesterolemia or cholesteryl ester storage disease have led these authors t propose that binding of LDL to high affinity cell surface receptor initiate the following vents After endocytosis of the lipoprotein and fusion of the endocytotic vesi l with lysosomes the apo B and cholesteryl esters are hydrolyzed by lysosomal enzymes The liberated cholesterol is reesterified by membrane bound fatty acyl coA cholesterol acyltransferase Rates of LDL uptake in the fibroblast may control the synthesis f both the LDL recepto and hydroxy methyl glutaryl coA reductase The latter is the rate limiting enzyme in chol sterol synthesis Regulation of this enzyme is complex however since it may also depend on rates of chol sterol efflux from the cell (Fogelman et al 1975; Edwards 1975)

These tissue culture tudi are consistent with the finding by Sniderman et al (1974) that functional hepatectomy in pigs increases the fractional cataboli rate f LDL. These authors proposed that the liver somehow serves to prolong the life of LDL. Plasma LDL are in rapid equilibrium with an extravascular mainly hepatic pool f LDL perhaps 2o-4o f the size f the intravascular pool Whether this hepati pool f LDL is extracellular membrane bound or intracellular is unknown are its possibl functions in LDL catabolism (Sniderman t al 1975)

Brown & Goldst in (1976) have proposed tha recepto -mediated non-hepati LDL degradation demonstrated in tissue culture studies is part f an in vivo net transport f cholesterol from the liver and small intestine to other tissues to cove requirements f membrane cholesterol At present this concept remains speculative and the major ite f LDL degradation in vivo is uncertain

Cholest rol transport to the live

Unesterified chol sterol exchanges between lipoproteins and cell membranes and Glomset (1972) has suggested that cholesterol est rification by LCAT promotes ne tran fe f cholesterol from non-hepati tissue cell to HDL circulating in interstitial fluids Since the liver may be the major site f HDL catabolism (Eisenberg Levy 197?) an important function f these lipoproteins could be transport f cholesterol to the liver fo excretion in bil or conversion to bil acids (Hill Miller 1975) Cultured hepatocytes vidly bind HDL (Breslov 1975) The previously discussed transfer f cholesteryl ters from HDL to VLDL chylomicrons or thei remnants may influence this transport howeve

HDL turnove time in the rat i long about 16 hour measured by following the

apoprotein moiety (Eisenberg & Levy 1975) compared to that of remnants about 7 minutes measured as VLDL components removed by the liver (Faergeman & Havel 1975) Since the content of LCAT derived cholesteryl esters in remnants destined for the liver is unknown transport rates cannot be calculated However the turnover times do suggest that in the rat substantial amounts of cholesterol from non-hepatic tissues could be transported to the liver by remnants Whether this also could be the case in the human is uncertain because a remnant pathway to the human liver has not been demonstrated experimentally The likelihood that human remnant metabolism nevertheless is qualitatively similar to that of experimental mammals (dog sheep rat) must be considered with the caution that always applies when extrapolating from one animal speci s to another

Concluding remarks

The role of the liver in controlling remnant catabolism and LDL formation the major in vivo ites and control of LDL catabolism and the control and transport functions of HDL are all important objects for further study As such they may form the basis for a better understanding particularly of the pathways of plasma cholesterol and phospholipid transport

A detailed understanding of the over all control of the plasma lipoproteins as a complex system for transporting water insoluble lipids will hopefully explain the various derangements of this system that caus human diseas

References

Alaupovi P Gustafson A Sardar S.S & Furman R.H Protein moi ties of human serum lipoproteins basis for classification Circulation 29-30 III I (suppl) 1964

Alaupovi P Conceptual development of the classification systems f plasma lipoproteins; pp 9-19 in Peeters H (ed) Protides f the Biological Fluids Pergamon Press Oxford & New York 1972

Assmann G. Mahley R W Davis B.D Holcombe K.S Cholesterol esterification by the rat live Golgi apparatus Sound J lin. Lab Invest 33 suppl 137 23-28 1974

Barter P.J Nestel P.J & Carroll K F Precursors f plasma triglyceride fatty acid in humans Eff cts of glucose consumption clofibrate administration and alcoholic fatty liver Metabolism 21 117 124 1972

Barte P J & Nestel P J Precursor-product relationship between pools f very low density lipoprotein triglyceride J clin Invest. 51 174 180 1972

Barter P J Origin f esterified chol terol transported in the very low density lipoproteins f human plasma J Lipid Res 15 11 19 1974

Barte P.J Connor W E The transport f triglyceride in the high-density lipoproteins of human plasma J Lab clin Med. 85 260-272 1975

Barte P Faergeman O & Havel R.J Metabolism of cholesteryl esters f very low density lipoproteins in the guinea pig Metabolism 1977 (in pres)

Belfrage P Metabolism f chyl triglycerides in the liver II Distribution f radioactivity between subcellular components afte the intravenous injection f glycerol and fatty cid-labeled chyle into the carbohydrate-fed rat. Biochim biophys Acta 152 264-279 1968

Bergman E.N Havel R.J Wolfe B.M. & Bøhmer T Quantitative tudies f the metabolism f chylomicron triglyc rides and cholesterol by liver and extra hepatic tissues f sheep and dogs J clin Invest 50 1831 1839 1971

Bersot Mahley R.W Brown M.S & Goldstein J L. Interaction f swine lipoproteins ith the low density lipoprotein receptor in human fibroblasts J biol Chem. 251 2395-2398 1976

Biggs M.W Studies on exogenous cholesterol metabolism in human therosclerosis with the aid f isotopes Adv biol med Phys 5 357-384 1957

Bilheimer D W Eisenberg S & Levy R.I The metabolism f very low density lipoprotein proteins I Preliminary in vitro and in vivo observations Biochim. biophys Acta 260 212 221 1972

Breslow J L. Spaulding D.R. & Lothrop D.A. Lipoprotein binding degradation and regul tion f st rol production in rat liver and fibroblast cell cul tures Circul tion 51 52 II 59 (suppl) 1975

Brewe J H.B Shulman R. Herbert P Ronan R. & Wehrly K The complete amino acid sequence f an apolipoprotein obtained from human very low density lipoprotein (VLDL) Adv exp Med Biol 26 280 1972

Brown M.S Goldstein J L Receptor-mediated control f cholesterol metabolism. Science 191 150-154 1976

apoprotein moiety (Eisenberg & Levy 1975) compared to that of remnants about 7 minutes measured as VLDL components removed by the liver (Faergeman & Havel 1975) Since the content of LCAT derived cholesteryl esters in remnants destined for the liver is unknown transport rates cannot be calculated However the turnover times do suggest that in the rat substantial amounts of cholesterol from non-hepatic tissues could be transported to the liver by remnants Whether this also could be th case in the human is uncertain because a remnant pathway to the human liver has not been demonstrated experimentally The likelihood that human remnant metabolism nevertheless is qualitatively similar to that of experimental mammals (dog sheep rat) must be considered with the caution that always applies when extrapolating from one animal species to another

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Hidex L.I. Rubain, P.S & Eder H.A. Turnover of cholesteryl esters f plasma lipoproteins in the rat J Lipid Res 8 7 15 1967
Gitlin D Cornwell D G Nakasato D Oncley J.L Hughe J W.L & Janeway C.A Studies on the metabolism of plasma proteins in the nephrotic syndrome II The lipoproteins J clin Invest 37 172 184 1958
Glomset J.A. Plasma lecithin cholesterol acyltransferase; pp 745-787 in Nelson G.J (ed.) Blood Lipids and Lipoproteins Quantitation Composition and Metabolism Wiley-Interscience New York 1972
Glomset J.A. Norum, K.R. Nichols A.V Forte T King W C Albers J Mitchell C.D Applegate K.R. & Gjone E Plasma lipoprotein metabolism in familial lecithin:cholesterol acyltransferase deficiency Scand. J clin. Lab Invest. 33 suppl 137 165-172 1974
Glueck C.J Ford J S Steiner P & Fallat R. Triglyceride removal efficiency and lipoprotein lipases ffects f oxandrolone Metabolism 22 807-814 1973
Goodman D.S The metabolism f chylomicron cholesterol ste in the rat J clin Invest 41 1886-1896 1962
Goodman D.S Cholesterol este metabolism. Physiol Rev 45 747-839 1965
Goodman E D & LaQuire V.S Transfer f esterified cholesterol from serum lipoproteins to the liver Biochim. biophys Acta 398 325-336 1975
Gotto A.M. Levy R.I John K. & Fredrickson D.S On the protein defect in abetalipoproteinemia New Eng J Med. 284 813-818 1971
Hamilton R L Synthesis and secretion of plasma lipoproteins Adv exp Med Biol 26 7 24 1972
Hamilton R.L Williams M.C Fielding C.J & Havel R.J Discoidal bilayer structure of nascent high density lipoproteins from perfused rat liver J clin. Invest. 58 667-680 1976
Havel R.J Conversion of plasma free fatty acids into triglycerides f plasma lipoprotein fractions in man Metabolism 10 1031 1034 1961
Havel R.J Felts J M & Van Duyne C.M Formation and fate of endogenous triglycerides in blood plasma f rabbits J Lipid Res 3 297 308 1962
Havel R.J Metabolism of lipids in chylomicrons and very low-density lipoproteins; pp 499-507 in Renold A E & Cahill J G.F (eds) Handbook of Physiology section 5 American Physiological Society Washington D C 1965
Havel R.J Kane J P Balasse E O Segel N Basso L.V Splanchnic metabolism f free fatty acids and production f triglycerides of very low density lipoproteins in normotriglyceridemi and hypertriglyceridemi humans J clin Invest 49 2017 2035 1970
Havel R.J Shore V C Shore B & Bier D.M. Role of specific glycopeptides f human serum lipoproteins in the activation f lipoprotein lipase Circulation Res 27 595-600 1970
Havel R.J Kane J.P Kashyap M.L. Interchange f apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipemia in man. J clin Invest 52 32 38 1973
Havel R.J Kane J P Primary dysbetalipoproteinemia predominance f specific apoprotein specie in triglyceride-rich lipoprotein Proc Nat Acad. Sci USA 7 2015-2019 1973
Havel R.J Lipoproteins and lipid transport. Adv exp Med. Biol 63 37-59 1975
Herbert P.N Windmueller H G. Bersot T P Shulman R.S Characterization f the rat polipoproteins I The low molecular weight proteins of rat plasma high density lipoproteins J biol Chem. 249 5718-5724 1974
Illingworth D R. Metabolism f lipoproteins in non-human primates Studies on the rigin f low density lipoprotein apoprotein in the plasma f the squirrel monkey Biochim. biophys Acta 388 38-51 1975
Jackson R.L. Morrisett J D & Gotto J A.M. Lipoprotein structure and metabolism. Physi l Rev 56 259-316 1976
Kane J P Richards E G & Havel R.J Subunit heterogeneity in human serum beta lipoprotein Proc Nat Acad. Sci USA 66 1075-1082 197
Kane J.P Hata T Hamilton R.L & Havel R.J Apoprotein composition of very low density lipoproteins f human serum J clin Invest. 56 1622-1634 1975
Kostne G. Studies on the cofactor requirements for lecithin:cholesterol acyl transferase Scand. J clin. Lab Invest 33 suppl 137 19-21 1974

Brunzell J D Hazzard W R Porte Jr D & Bierman E L Evidence for a common saturable triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man *J clin Invest* 52 1578-1585 1973
Deckelbaum R J Shipley G.G Small D M Lees R S & George P.K Thermal transitions in human plasma low density lipoproteins Science 19o 392 394 1975
Edwards P A Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in rat hepatocytes by lipoproteins and lipid dispersions Circulation 51 52 II 271 (suppl) 1975
Ehnholm C Huttunen J K Kinnunen P J Miettinen T A & Nikkilä E.A Effect of oxandrolone treatment on the activity of lipoprotein lipase hepatic lipase and phospholipase A_1 of *human postheparin plasma New Eng* J Med 292 1314 1317 1975
Eisenberg S Bilheimer D W Levy R I & Lindgren F T On the metaboli conversion of human plasma very low density lipoprotein to low density lipoprotein Biochim biophys Acta 326 361-377 1973
Eisenberg S & Rachmilewitz D Metabolism of rat plasma very low density lipoprotein I Fate in circulation of the whole lipoprotein Biochim biophys Acta 326 378-39o 1973
Eisenberg S & Levy R.I Lipoprotein metabolism Adv Lipid Res 13 1-89 1975
Eisenberg S & Rachmilewitz D Interaction of rat plasma very low density lipoprotein with lipoprotein lipase-rich (postheparin) plasma J Lipid Res 16 341-351 1975
Eisenberg S & Schurr D Phospholipid removal during degradation of rat plasma very low density lipoprotein in vitro J Lipid Res 17 578-587 1976
Elovson J Olivecrona T & Belfrage P Metabolism in the rat of chyle obtained after feeding hydrogenated coconut oil labeled with teari acid Biochim biophys Acta lo6 34-44 1965
Faergeman O & Damgaard-P dersen F Increase of postheparin lipase activity by oxandrolone in familial hyperchylomicronemia Scand J clin Lab Invest 31 27 31 1973
Fa rgeman O & Havel R J Metabolism of chol teryl esters of rat very low density lipoproteins J clin Invest 55 121o-1218 1975
Faergeman O Sata T Kane J P & Havel R.J Metabolism of poprotein B f plasma very low density lipoproteins in the rat J clin Invest 56 1396-14o3 1975
Fidge N H & Foxman C J In vivo transformation of rat plasma very *low density* lipoprotein into higher density lipoproteins Aust J exp Biol med Sci 49 581 593 1971
Fidge *N H & Poulis P Studies on the radioiodination of very low dens ty* lipoprotein obtained from different mammalian species Clin chim Acta 52 15-26 1974
Fielding C J *Shore* V G & *Fielding* P E A protein cofactor of lecithin cholesterol acyltransferase Biochim biophys Res Comm 46 1493-1498 1972
Fielding C J & Higgins J M Mechanism of formation of triglyceride-rich remnant particles from very low dens ty lipoproteins in the perfused rat heart Fed Proc 33 351 1974
Fogelman A M S ager J Edmond J & Popjak G Abnormal efflux of cholesterol from heterozygous familial hyperchole terolemi l ukocytes Circul tion 51 52 II-81 (suppl) 1975
Forte T Nichol A Glom t J & Norum K The ultrastructure of plasma lipoproteins in lecithin chol sterol acyltransferase defi iency Scand J clin Lab Invest 33 suppl 137 121 132 1974
Fredrickson D S & Gordon Jr R.S Transport of fatty a ids Physiol Rev 38 585-63o 1958
Gangl A & Ockner R.K *Intestinal metabolism of lipids and lipoproteins* Gastroenterology 68 167 186 1975
Garner Jr C W Smith L C Jackson R L & Gotto Jr A M. Stimulation of lecithin cholesterol acyl transferase by plasma apolipoproteins Circulation 45-46 II 246 (suppl) 1972
Gidez L I Roheim P S & Eder H A Effect of di t on the cholesterol ester composition of liver and of plasma lipoproteins in the rat J Lipid Res 6 377 382 1965

Gidez L.I Roheim, P S & Eder H.A. Turnover of cholesteryl esters of plasma lipoproteins in the rat J Lipid Res 8 7 15 1967
Gitlin D Cornwell D G Nakasato D Oncley J L, Hughes J W L. & Janeway C.A Studies on the metabolism f plasma proteins in the nephrotic syndrome II The lipoproteins J clin. Invest 37 172 184 1958
Glomset J.A. Plasma lecithin cholesterol acyltransferase; pp 745-787 in Nelson G.J (ed) Blood Lipids and Lipoproteins Quantitation Composition and Metabolism. Wiley-Interscience New York 1972
Glomset J.A. Norum K.R. Nichols A.V Forte T King W C Albers J Mitchell C.D Applegate K.R. & Gjone E Plasma lipoprotein metabolism in familial lecithin cholesterol acyltransferase deficiency Scand J clin Lab Invest 33 suppl 137 165-172 1974
Glueck C.J Ford J S Steiner P & Fallat R. Triglyceride removal efficiency and lipoprotein lipases ffects of oxandrolone Metabolism 22 807-814 1973
Goodman D S The metabolism of chylomicron cholesterol ester in the rat. J clin Invest 41 1886-1896 1962
Goodman D.S Cholesterol ester metabolism Physiol Rev 45 747-839 1965
Goodman E D & LeQuire V S Transf f esterified cholesterol from serum lipoproteins to the liver Biochim. biophys Acta 398 325-336 1975
Gotto A.M. Levy R.I John K. & Fredrickson D.S On the protein defect in abetalipoproteinemia New Eng J Med. 284 813-818 1971
Hamilton, R.L Synthesis and secretion of plasma lipoproteins Adv exp Med. Biol 26 7 24 1972
Hamilton R.L Williams M C Fielding C.J & Havel R.J Discoidal bilayer structure f nascent high density lipoproteins from perfused rat liver J lin. Invest 58 667-680 1976
Havel R.J Conversion f plasma free fatty acids into triglycerides of plasma lipoprotein fractions in man Metabolism 10 1031 1 34 1961
Havel R.J Felts J.M. & Van Duyne C.M Formation and fate f endogenous triglycerides in blood plasma f rabbits J Lipid Res 3 297 308 1962
Havel R.J Metabolism f lipids in chylomicrons and very low-density lipoproteins; pp 499-507 in Renold A.E & Cahill J G.F (eds) Handbook f Physiology section 5 American Physiological Society Washington D C 1965
Havel R.J Kane J P Balasse E O Segel N & Basso L.V Splanchnic metabolism f free fatty acids and production f triglycerides f very low density lipoproteins in normotriglyceridemi and hypertriglyceridemic humans J clin. Invest 49 2017-2035 1970
Havel R.J Shore V G Shore B & Bie D M Role of specific glycopeptide f human serum lipoproteins in the activation f lipoprotein lipase Circulation Res 27 595-600 1970
Havel R.J Kane J P & Kashyap M.L. Interchange f apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipemia in man. J clin. Invest 52 32 38 1973
Havel R.J Kane J.P Primary dysbetalipoproteinemia predominance f a specifi apoprotein species in triglyceride-rich lipoproteins Proc Nat Acad. Sci USA 70 2015-2019 1973
Havel R.J Lipoproteins and lipid transport Adv exp Med Biol 63 37-59 1975
Herbert P.N Windmueller H G. Bersot T.P & Shulman R.S Characterization f the rat polipoproteins I The low molecular weight proteins of rat plasma high density lipoproteins J bi l Chem 249 5718-5724 1974
Illingworth D R. Metabolism f lipoproteins in non-human primates Studies on the origin f low density lipoprotein apoprotein in the plasma of the squirrel monkey Biochim. biophys Acta 388 38-51 1975
Jackson R.L. Morrisett J D & Gotto J A M Lipoprotein structure and metabolism. Physiol Rev 56 259-316 1976
Kane J P Richards E G & Havel R.J Subunit heterogeneity in human serum beta lipoprotein Proc Nat Acad. Sci USA 66 1075-1082 197
Kane J P Sata T Hamilton R.L Havel R.J Apoprotein composition of very low density lipoproteins f human serum. J lin Invest. 56 1622 1634 1975
Kostner G Studies on the cofactor requirements for lecithin:cholesterol acyl transferase Scand. J clin Lab Invest 33 suppl 137 19-21 1974

Brunzell J D Hazzard W R Porte Jr D & Bierman E L Evidence for a common saturable triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man J clin Invest 52 1578-1585 1973
Deckelbaum R J Shipley G G Small D M Lees R.S & George P K Thermal transitions in human plasma low density lipoproteins Science 19o 392 394 1975
Edwards P A : Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductas activity in rat h patocytes by lipoproteins and lipid dispersions Circulation 51-52 II-271 (suppl) 1975
Ehnholm C Huttunen J K Kinnunen P J Miettinen T A & Nikkilä E A Effect of oxandrolone treatment on the activity of lipoprotein lipase hepatic lipase and phospholipase A_1 of human postheparin plasma New Eng J Med 292 1314 1317 1975
Eisenberg S Bilheimer D W Levy R.I & Lindgren F T On the metabolic conversion of human plasma very low density lipoprotein to low density lipoprotein Biochim biophys Acta 326 361 377 1973
Eisenberg S & Rachmilewitz D Metabolism of rat plasma very low density lipoprotein I Fate in circulation of the whole lipoprotein Biochim biophys Acta 326 378-39o 1973
Eisenberg S & Levy R.I Lipoprotein metabolism Adv Lipid Res 13 1-89 1975
Eisenberg S & Rachmilewitz D Interaction of rat plasma very low density lipoprotein with lipoprotein lipase-rich (postheparin) plasma J Lipid Res 16 341-351 1975
Eisenberg S & Schurr D Phospholipid removal during degradation of rat plasma very low density lipoprotein in vitro J Lipid Res 17 578-587 1976
Elovson J Olivecrona T & B lfrage P Metabolism in the rat of chyl obtained after feeding hydrogenated coconut oil labeled with stearic acid Biochim. biophys Acta 1o6 34-44 1965
Faergeman O & Damgaard-Pedersen F Increase of postheparin lipase activity by oxandrolone in familial hyperchylomicronemia Scand J clin Lab Invest 31 27 31 1973
Faergeman O & Havel R J Metabolism of cholesteryl esters of rat very low density lipoproteins J clin Invest 55 121o-1218 1975
Faergeman O Sata T Kane J P & Havel R J Metabolism of apoprotein B of plasma very low density lipoproteins in the rat J clin Inve t 56 1396-14o3 1975
Fidge N H & Foxman C J In vivo transformation of rat plasma very low density lipoprotein into higher density lipoprotein Aust J exp B ol med Sci 49 581 593 1971
Fidge N H & Poulis P Studies on th radioiodination of very low density lipoprotein obtained from diff rent mammalian species Clin chim Acta 52 15 26 1974
Fielding C J Shore V G & Fielding P E A protein cofactor of lecithin cholesterol acyltransferase Biochim biophys Res Comm 46 1493-1498 1972
Fielding C J & Higgins J M Mechanism of formation of triglyceride-rich remnant particles from very low density lipoproteins in th perfused rat heart Fed Proc 33 351 1974
Fogelman A M. Seager J Edmond J & Popjak G Abnormal fflux of cholesterol from heterozygous familial hypercholesterolemic leukocytes Circul tion 51-52 II 81 (suppl) 1975
Forte T Nichol A Glom t J & Norum K The ultrastructure f plasma lipoproteins in le ithin chol sterol acyltransf ras defi iency Scand J clin Lab Invest 33 suppl 137 121 132 1974
Fredrickson D S & Gordon Jr R S Transport of fatty acids Physiol Rev 38 585-63o 1958
Gangl A & Ockner R.K I testinal metabolism of lipids and lipoproteins Gastroenterology 68 167-186 1975
Garner Jr C W Smith L C J ckson R L & Gotto Jr A M Stimulation of lecithin cholesterol acyl transf rase by plasma apolipoproteins Circulation 45-46 II 246 (suppl 1 1972
Gidez L I Roh im P S & Eder H.A Effect of diet on the cholesterol ster composition of liver and of plasma lipoproteins in the rat J Lipid Res 6 377-382 1965

Gidez L.I Roheim P.S & Eder H.A. Turnover of cholesteryl esters of plasma lipoproteins in the rat J Lipid Res 8 7 15 1967

Gitlin D Cornwell D G Nakasato D Oncley J.L. Hughes Jr W.L. & Janeway C.A. Studies on the metabolism of plasma proteins in the nephrotic syndrome II The lipoproteins J clin Invest 37 172 184 1958

Glomset J.A. Plasma lecithin:cholesterol acyltransferase; pp 745-787 in Nelson G.J (ed.) Blood Lipids and Lipoproteins Quantitation Composition and Metabolism Wiley-Interscience New York 1972

Glomset J.A. Norum, K.R. Nichols A.V Forte T King W C Albers J Mitchell C.D Applegate K.R. & Gjone E Plasma lipoprotein metabolism in familial lecithin cholesterol acyltransferase deficiency Scand. J lin Lab Invest 33 suppl 137 165-172 1974

Glueck C.J Ford J S Steiner P & Fallat R. Triglyceride removal efficiency and lipoprotein lipases ffects of oxandrolone Metabolism 22 807-814 1973

Goodman D.S Th metabolism of chylomicron cholesterol este in the rat J clin Invest 41 1886-1896 1962

Goodman D.S Cholesterol este metabolism. Physiol Rev 45 747-839 1965

Goodman S D & LeQuire V.S Transf r f esterified cholesterol from serum lipoproteins to the liver Biochim. biophys Acta 398 325-336 1975

Gotto A.M. Levy R.I John K. & Fredrickson D.S On the protein defect in abetalipoproteinemia New Eng J Med. 284 813-818 1971

Hamilton R.L. Synthesis and secretion of plasma lipoproteins Adv exp Med. Biol 26 7 24 1972

Hamilton, R.L Williams M.C Fielding C J & Havel R.J Discoidal bilayer structure of nascent high density lipoproteins from perfused rat liver J clin Invest 58 667-680 1976

Havel R.J Conversion f plasma free fatty acids into triglycerides of plasma lipoprotein fractions in man Metabolism 10 1031 1 34 1961

Havel R.J Felts J M. Van Duyne C M. Formation and fate of endogenous triglycerides in blood plasma f rabbits J Lipid Res 3 297 308 1962

Havel R.J Metabolism of lipids in chylomicrons and very low-density lipoproteins; pp 499-507 in Renold A.E & Cahill J G.F (eds) Handbook of Physiology section 5 American Physi logical Society Washington D C 1965

Havel R.J Kane J P Balasse E O Segel N & Basso L.V Splanchnic metabolism of free fatty acids and production f triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans J clin. Invest 49 2017-2035 1970

Havel R.J Shore V G Shore B & Bier D M Rol of specific glycopeptides of human serum lipoproteins in the activation of lipoprotein lipase Circulation Re 27 595-600 1970

Havel R.J Kane J.P & Kashyap M.L Interchange f apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipemia in man J clin Invest 52 32 38 1973

Havel R J & Kane J P Primary dysbetalipoproteinemia predominance f a specific apoprotein species in triglyceride-rich lipoproteins Proc Nat. Acad. Sci USA 70 2015-2019 1973

Havel R.J Lipoproteins and lipid transport. Adv exp Med. Biol 63 37 59 1975

Herbert, P.N Windmueller H G Bersot T.P & Shulman R.S Characterization of the rat apolipoproteins I The low molecular weight proteins of rat plasma high density lipoproteins J biol Chem. 249 5718-5724 1974

Illingworth D.R. Metabolism f lipoproteins in non-human primates Studies on the origin f low density lipoprotein apoprotein in the plasma of the squirrel monkey iochim. biophys Acta 388 38-51 1975

Jackson R.L. Morrisett J D & Gotto J A.M Lipoprotein structure and metabolism. Physiol Rev 56 259-316 1976

Kane J P Richards E G. & Havel R.J Subunit heterogeneity in human serum beta lipoprotein Proc Nat Acad. Sci USA 66 1075-1082 197

Kane J.P Sata T Hamilton R.L. Havel R.J Apoprotein composition of very low density lipoproteins f human serum. J clin Invest 56 1622 1634 1975

Kostner G. Studies on the cofactor requirements for lecithin:cholesterol acyl transferase Scand. J clin Lab Invest 33 suppl 137 19-21 1974

LaRosa J C Levy R I Herbert P Lux S.E & Fredrickson D S A specific apoprotein activator for lipoprotein lipase Biochim biophys Res Comm. 41 57-62 197o
Lossow W J Brot N & Chaikoff I L Disposition of the cholesterol moiety of a chylomicron-containing lipoprotein fraction of chyle in the rat J Lipid Res 3 2o7-215 1962
Margolis S & Capuzzi D Serum-lipoprotein synthesis and metabolism; pp 825-88o in Nelson G J (ed) Blood Lipids and Lipoproteins Quantitation Composition and Metabolism Wiley-Intersci nce New York 1972
Miller G J & Miller N E Plasma-high-density lipoprotein concentration and development of ischemic heart-disease Lancet I 16-19 1975
Mjøs O D Fa rgeman O Hamilton R L & Havel R J Characterization of remnants produced during the metabolism of triglyceride-rich lipoproteins of blood plasma and intestinal lymph in the rat J clin Invest 56 6o3-615 1975
Nestel P J Havel R J & Bezman A Metabolism of constituent lipids of dog chylomicrons J clin Invest 42 1313-1321 1963
Nestruck A C & Rubinstein D The acquisition of C peptides by nascent VLDL during passage through the Golgi apparatus of rat liver Circulation 51 52 II 274 (suppl) 1975
Nikkilä E A : Control of plasma and liver triglyceride kinetics by carbohydrate metabolism and insulin Adv Lipid Res 7 63-134 1969
Nilsson-Ehl P Carlström S & Belfrage P Rapid ffects on lipoprotein lipase activity in adipose tis ue of humans after carbohydrate and lipid intak Scand J clin Lab Invest 35 373-378 1975
Noel S -P & Rubin tein D Secretion of apolipoproteins in very low density and high density lipoproteins by perfused rat liver J Lipid Res 15 3o1-3o8 1974
Norum K R. Oppbygning og metabolisme av sirkulerende lipoproteiner Nord Med 86 1173-1179 1971
Olivecrona T & Belfrage P Mechanisms for removal of chyle triglyceride from the circulating blood as studied with [^{14}C] glycerol and [^{3}H] palmitic acid-labeled chyle Biochim biophys Acta 98 81 93 1965
Olofsson S -O & Gustafson A Degradation of h gh-density lipoprotein (HDL) in vitro Scand J clin Lab Invest 33 suppl 137 57-62 1974
Olofsson S -O Studies on human serum high density lipoproteins (HDL) Göteborg 1975 (thesis)
Phair R D Hammond M G Bowden J A Fri d M Fisher W R & Berman M A preliminary model for human lipoprotein metabolism in hyperl poproteinemia Fed Proc 34 2263-227o 1975
Pierce Jr F T Th interconversion of serum l poproteins in vivo Metabolism 3 142-153 1954
Quarfordt S H & Goodman D S Metabolism of doubly-label d chylomi ron cholesteryl esters in the rat J Lipid Res 8 264 273 1967
Quarfordt S H & Goodman D S Chylomicron cholesteryl ter metabol sm in th perfused rat liver Biochim biophys Acta 176 863-872 1969
Quarfordt S.H Frank A Shames D M Berman M & St inberg D Very low density lipoprotein triglycer de transport in type IV hyperlipoproteinemi and the ffects of carbohydrate-rich di ts J lin Invest 49 2281 2297 197
Redgrave T G Formation of chol st ryl est r rich particulate lip d during metabolism of chylomicrons J lin Inve t 49 465-471 197
Roheim P S Edelstein D I Vega G & Eder H A Metabolism of very low dens ty apolipoproteins in ucrose fed hyperl pemic rats Fed Proc 32 672 Abs 1973
Roe H G Origin of cholesteryl est rs in the blood of cholesterol fed rabb ts relative contributions f serum lec thin-ch l sterol cyltransf as and hepatic ester synthe is B ochim bi phys Acta 26o 312 326 1972
Rubenstein B & Rubinstein D I terrel tionsh p between rat serum very low density and high density lipoproteins J Lip d Res 13 317 3 4 1972
Rudel L.L Morris M D & Felts J M The transport of exogenous cholesterol th rabbit I Rol of cholesterol este of lymph chylomicra and lymph very low density lipoproteins in absorption J clin I ve t 51 2686-2692 1972

Sata, T Havel R.J & Jones A L. Characterization of subfractions of triglyceride-rich lipoproteins separated by gel chromatography from blood plasma of normolipemic and hyperlipemic humans J Lipid Res 13 757 768 1972

Schumaker V N & Adams G H Very low density lipoproteins surface-volume changes during metabolism J theoret Biol 26 89-91 1970

Sherrill B C & Dietschy J.M. Uptake f lipoproteins f intestinal rigin in the isolated perfused liver Circulation 53-54 II-91 (suppl) 1976

Shore V G. & Shore B The apolipoproteins their structure and functional roles in human-serum lipoproteins; pp 789-824 in Nelson G J (ed.) Blood Lipids and Lipoproteins Quantitation Composition and Metabolism. Wiley-Interscience New York 1972

Shore V G. Shore B & Hart R.G. Changes in apolipoproteins and properties of rabbit very low density lipoproteins on induction f cholesteremia Biochemistry 13 1579-1585 1974

Shulman R. Herbert P Wehrly K Chesebro B Levy R I & Fredrickson, D.S The complete amino acid sequence f apoLP-ser an apolipoprotein obtained from human very low density lipoprotein Circulation 45-46 II 246 (suppl) 1972

Sigurdsson G Nicoll A & Lewis B Conversion f very low density lipoprotein to low density lipoprotein A metaboli study f apolipoprotein B kinetics in human subjects J clin Invest 56 1481 1490 1975

Skipski V P Lipid composition f lipoproteins in normal and diseased tates; pp 471 583 in Nelson G J (ed) *Blood Lipids and Lipoproteins Quantitation Composition and Metabolism* Wiley-Interscience New York 1972

Smith R. Dawson J R. & Tanford C The size and number f polypeptide chains in human serum low density lipoprotein J biol Chem. 247 3376-3381 1972

Sniderman A D Carew T E Chandler J G & Steinberg D Paradoxical increase in rate f catabolism f low-density lipoproteins afte hepatectomy Science 183 526-528 1974

Sniderman A.D Carew T.E & Steinberg D Turnove and tissue distribution f ^{125}I labeled low density lipoprotein in swine and dogs J Lipid Res 16 293-299 1975

Stein O & in Y Goodman D S & Fidge N H The metabolism of chylomicron cholesteryl este in ra live J Cell Biol 43 410-431 1969

Stein O Rachmilewitz D Sanger L Eisenberg S Stein Y Metabolism f iodinated very low density lipoprotein in the rat. Autoradiographic locali zation in the liver Biochim. biophys Acta 360 205-216 1974

Stein Y Ebin V Bar-on H Stei O Chloroquine-induced interference with degradation f serum lipoproteins i rat live studied in vivo and in vitro Biochim. biophys Acta 486 286-297 1977

Stokke K T The existence f an acid cholest rol esterase in human liver Biochim. biophys Acta 270 156-166 1972

Wieland, H Ganesan D McConathy W.J Alaupovi P Changes in lipoproteins and diff rential release f C-I ($LPL_{C\ I}$) and C II ($LPL_{C\ II}$) activated lipoprotein l pases i postprandial stat f normal human subjects Circulation 51-52 II 39 (suppl) 1975

Windmueller H G Herbert P N Levy R.I Biosynthesis f lymph and plasma lipoprotein apoproteins by isol ted perfused rat live and intestine J Lipid Res 14 215 223 1973

Zilversmit D B The surface coat f chylomicrons lipid chemistry J Lipid Res 9 180-186 1968

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Supplementum 616

Non-invasive detection of critical coronary lesions potentially associated with sudden death

Annex
Mexiletine effect on the monophasic action potential (MAP) of right ventricle in man

Symposium Goteborg 19th September 1977

Edited by Ed Varnauskas

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1.

INTRODUCTION

Ed Varnauskas

1.

INTRODUCTION

Ed Varnauskas

Improved survival following coronary artery bypass surgery in patients with main stem disease re-emphasizes the well established relationship between prognosis and the extent and severity of coronary arteriosclerotic lesions. Critical degree and localization of the stenosis may highly influence the longevity. This stimulates the search for a possible anatomical correlation with sudden death. Establishment of such a correlation might considerably enhance the possibilities to prevent sudden death by adding coronary bypass surgery to other preventive measures.

There are no absolute methods short of arteriography to visualize obstructive lesions in coronary arteries. The shortcomings of coronary arteriography such as cost, risk of serious complications etc. do not permit, however the use of this invasive procedure as a screening method. The non-invasive methods are therefore highly desirable to define the candidate for coronary arteriography.

The present symposium is devoted to discussions of the evidence suggesting a close association between specified critical coronary lesions and sudden death and also to assessment of the possibilities of predicting such lesions from non invasive investigations.

It is a great pleasure for me to thank the renowned investigators for cooperation in presenting their work at the symposium and their manuscripts for this publication.

One manuscript was not submitted. A contribution by J. Carlsson-Ejdebäck et al. is included although it was not presented at the symposium. This inclusion is motivated by the relevance of the contribution to the subject discussed.

The symposium was held in association with the annual working meeting of the European Coronary Bypass Study Group. I am pleased to acknowledge that both the symposium and the meeting were generously supported by Boehringer Ingelheim. Desmond Julian and Edgar Sowton acted as chairmen of the symposium.

Ed Varnauskas

2.

THE ANGIOGRAPHIC DEFINITION OF CRITICAL CORONARY STENOSIS

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Wilmer W. Nichols, Ph.D

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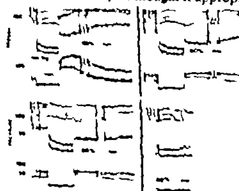
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6 NIH Research Grant No NIH HL-17717

Dr Feldman is a Research Fellow of the Florida Heart Association

coronary blood flow (electromagnetic transducer) were measured at rest and llowing a 10 second coronary artery occlu-

The upper left panel represents resting ᴬ reactive hyperemic coronary blood flow a non-obstructive coronary artery There is pressure gradient from aorta to distal coronary artery Following a 10 second occlu- there is a small pressure differential and typical hyperemic response. The upper panel illustrates the effect of a 60 % lu diameter reduction produced by a ... snare occlusion. There is no di ution of resting coronary blood flow and is no resting pressure gradient. Follow g a 10 second coronary occlusion there is a ... in the peak reactive hyperemic re- onse and a clear cut pressure differential aorta to distal coronary artery In the wer left panel the effect of an 80 % snare rrowing is represented. There was no rest aorta-coronary gradient nor was there , decrease in resting coronary blood flow llowing a 10 second occlusion there is mar decrease in the peak hyperemic response a large pressure differential between ... and distal coronary artery In the lower panel a 90 % snare narrowing produces ...ed decrease in resting coronary blood and a resting aorta coronary pressure adient. Following 10 second coronary ar occlusion reactive hyperemia is essentially obliterated and the aorta-coronary pressure gradient is increased.

Since a 60 % lumen diameter reduction oduced by a snare, had little effect on rest coronary blood flow and began to dimin the peak reactive hyperemic response to a second occlusion, we thought it appropri



...ure 3 *Effect of length of a coronary narrowing on coronary artery blood flow and pressure (see text)*

ate to evaluate the effect of lengthening the 60 % narrowings on coronary blood flow Figure 3 illustrates the effect of lengthening a 60 % lumen diameter reduction on resting coronary blood flow distal coronary artery pressure and the peak reactive hypremic response. The upper left panel shows the effect of a 1 mm long 60 % narrowing. There was no difference between the narrowing and the 60 % snare occlusion shown in Figure 2. Upper right panel increasing the length of this 60 % narrowing to 5 mm, produces a striking increase in the resting aorta coronary pressure gradient and a slight decrease in resting coronary blood flow The peak reactive hyperemic response is markedly decreased. Lower left panel increasing the length of the 60 % narrowing to 10 mm decreases the resting coronary blood flow and essentially obliterates the reactive hyperemic response. (Comparable to a 90 % lumen diameter reduction produced by a snare, shown in Figure 2.) Lower right panel the 60 % narrowing 15 mm long practically obliterates resting coronary blood flow and produces a marked pressure gradient. This occluder had to be removed quickly for obvious reasons.

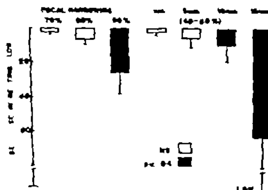


Figure 4 Effect of percent narrowing and length of narrowing on resting coronary blood flow (see text)

Figure 4 summarizes the percent decrease in resting coronary blood flow in the group of eight animals studied. To the left of the figure are illustrated the effects of 70 80 and 90 % narrowings produced by snare. It is obvious that a 90 % narrowing produced the greatest reduction in resting coronary blood flow whereas a 70 % narrowing had little effect. To the right of the figure are summarized data on the effect of increasing the length of 40 – 60 % coronary artery narrowings. It is obvious that

The primary goal of coronary angiography is to identify sites of critical reduction in coro nary artery lumen sufficient to produce myocardial ischemia. The human angiographer is faced with the problem "what is the physiologic significance of a coronary artery narrowing observed during angiography?" Gould et al and Lawrie et al have shown that a reduction in lumen diameter of 80 % or greater will reduce resting coronary blood flow in the laboratory animal (1,2) These observations have been extended to the human situation and have led to the view that an 80 % reduction in lumen diameter is sufficient to result in myocardial ischemia in the resting heart and certainly in the stressed heart.

Clinical observations in patients suggest that a coronary artery diameter reduction of less than 80 % may be sufficient to result in myocardial ischemia, particularly during periods of stress. Experimental studies in an animal model by Gould and Lipscomb (3) and Hillis and Freisinger (4) support the view that a 50 % reduction in lumen diameter may be sufficient to reduce coronary blood flow particularly during periods of increased demands.

Experiments in our laboratory confirm and extend the observations of Gould and Freisinger In this communication we want to make three major points by developing three separate but related experiments. First coronary artery blood flow studies in an animal model to show that a long coronary artery narrowing or sequential coronary narrowing, affect resting and peak hyperemic coronary blood flow more than short or single narrowings. Second angiographic studies of coronary artery narrowings of known length and percent lumen diameter reduction in an animal model to show that coronary angiography is most accurate when the coronary artery narrowing is trivial or severe greater than 5 mm in length or when the narrowing is measured with calipers. Third, angiographic studies of the effect of nitroglycerin on percent lumen diameter reduction in man to show that nitroglycerin may alter the angiographic estimation of percent coronary lumen diameter reduction

I CORONARY ARTERY BLOOD F… STUDIES IN AN ANIMAL MODEL

(A) The effect of the Percent Narrowing Length of Coronary Artery Narrowing o… Resting and Reactive Hyperemic Coro… Blood Flow

Coronary narrowings were created … anesthestized open-chest dogs using a cal… ibrated snare or Milled plastic occluders Aortic and distal coronary pressures … constantly monitored Figure 1 is a left … rior oblique projection of a left coronary ar…

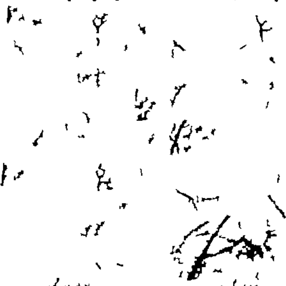


Figure 1 Angiographic appearance of narrowi… created by Milled plastic occluder (… text)

giogram to illustrate the angiographic a… pearance of a 60 % lumen diameter reducti… produced by a 1 5 10 and 15 mm long Mill… plastic occluder

A typical experiment in a single anim… study is illustrated in Figure 2 In this exp… riment aortic and distal coronary pressu…

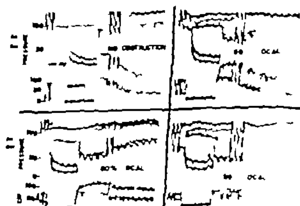


Figure 2 Effect of snare coronary narrowings on coronary artery blood flow and pre…ure (see text)

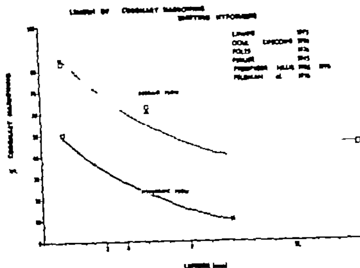


Figure 7 Comparison of different studies on the effect of length on resting and reactive hyperemic coronary blood flow (see text)

) Conclusion

data indicate the following. First, short of 40—60 % do not decrease rest coronary blood flow but slightly decrease hyperemic coronary blood flow. Sec d increasing the length of these 40—60 % from 1 to 5 mm further decreases peak hyperemic coronary blood flow re Third, increasing the length of 40— % narrowings to 10 mm decreases resting ronary blood and obliterates reactive coronary blood flow. Fourth, se al narrowings of 40—60 % decreased ak hyperemic coronary blood flow greater single narrowings of the same total

PROBLEMS ASSOCIATED WITH ANGIOGRAPHIC ASSESSMENT OF ARTERY NARROWINGS OF NOWN LENGTH AND PERCENT MEN DIAMETER REDUCTION

ly in the course of our animal experience, noted that the angiographic assessment of short narrowing (of proven severity) was sually interpreted as a much higher degree narrowing. For example, a 60 % narrow 1 mm in length appeared to be an 80— coronary artery narrowing. As a result these causal observations, an experiment as designed in which angiograms of the coronary arteries of animals, with known degree of narrowing and known length of nar rowing were evaluated by two independent angiographers.

(A) Subjective and Objective Assessment of Coronary Angiograms

Coronary angiograms of 50 coronary ar tery narrowings were evaluated by two expe-

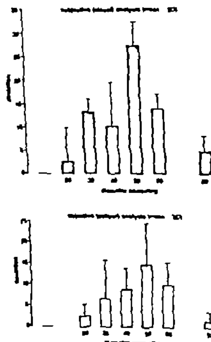


Figure 8 Accuracy of subjective and objective analysis of coronary angiograms (see text)

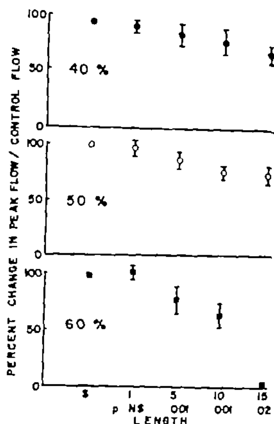


Figure 5 Effect of percent narrowing and length of narrowing on peak reactive hyperemia (see text)

as the length of the coronary narrowing in creases resting coronary blood flow decreases Similar results were obtained during reactive hyperemia as illustrated in Figure 5 In this illustration peak hyperemic flow is divided by control flow in order to normalize the response for each individual animal. The top panel illustrates the effects of a 40 % nar rowing. As the points go from left to right the length of the coronary narrowing increases from the snare narrowing to a 15 mm long narrowing. It is obvious that as the length of the narrowing increases the peak reactive hyperemic response decreases in the 40 50 and 60 % narrowings. The effect is most strik ing with 60 % narrowings.

(B) The Effect of Sequential Coronary Artery Narrowings on Resting and Peak Reactive Hyperemic Coronary Blood Flow

Preliminary experiments have been perfor med in which we compared the effect of a 60 % narrowing 2 mm in length to a series of two 60 % narrowings 1 mm in length. Figure 6 illustrates this comparison in a single ani mal study The left panel shows no resting aorta-coronary pressure gradient and normal resting coronary blood flow Following a 10

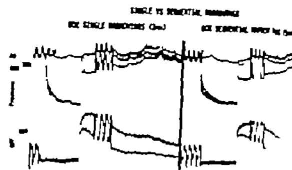
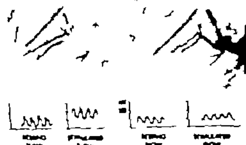


Figure 6 Effect of sequential coronary artery na rowing on resting and peak reactive hy remic coronary blood flow (see text)

second occlusion a slight aorta- pressure gradient develops and there is a pical reactive hyperemic response. The ri panel shows an unchanged resting coronar blood flow but a slight resting aorta- pressure gradient. Following a 10 second clusion there is a clear cut aorta-co pressure gradient and a slight decrease of peak reactive hyperemic response. We ha found this observation to be consistent in small number of animals that have been s died. The explanation for this effect is n clear at the moment.

(C) Summary

Figure 7 summarizes our own data and com pares it to that of others (5 6 7) The area contains data obtained during reactiv hyperemia. Vertical axis represents the de gree of coronary narrowing that was required to decrease coronary blood flow from con trol Horizontal axis represents the length of the coronary narrowing. The dotted line resents the best fit curve for our data. T dashed line represents the best fit curve for resting coronary blood flow published b others. The solid line in the hatched area is best fit curve for all data during reactive hyperemia. The data indicate that as the length of the coronary narrowing increases the percent narrowing required to resting coronary blood flow decreases. example, an 85 % narrowing, 1 mm in length will reduce resting coronary blood flow whereas a 55 % narrowing requires a length of 10 mm to have the same effect on resti coronary blood flow The hatched area contains similar data during hyperemic coronary blood flow and again illustrates the striking effect of increasing the length of the narrow ing on the reactive hyperemic response



...ure 12 Coronary angiogram of a 70% narrowing 1 mm and 5 mm in length (see text)

panel) and 5 mm long (right panel). Nor ...l resting and peak stimulated flow is pre... in the 1 mm long narrowing and there is ...light alteration of resting blood flow and ...ked decrease in peak stimulated blood ...w in 5 mm long narrowing. Figure 12 strik...ly illustrates the discrepancy between the ... perception of the degree of narrowing ... the actual degree of narrowing, measu... postmortem in an artery with a 70% ...owing of 1 mm length (left panel) and 5 ... length (right panel). Resting and peak ...lated flows are slightly decreased in the ... long narrowing and markedly dimi...ned in the 5 mm narrowing. Note the im...diate appearance of collateral blood flow ...m the left anterior descending coronary ...y to the marginal branches of the circum... in the right panel, at the arrow. Imme...ite appearance of collateral blood flow to ... distal marginal branch emphasizes, in this ... the physiologic abnormality produ... by the longer narrowing.

...) Conclusion

...foregoing observations relating to obser... accuracy with coronary angiography can ... summarized as follows. Errors are greatest ... of 40 – 60% lumen diameter ...on, narrowings of less than 5 mm in ... and with subjective estimates of coro...y artery narrowings. Errors are least with ...ial or severe narrowings, narrowings ... than 5 mm in length and narrowings ...ured with callipers.

III. PROBLEMS ASSOCIATED WITH THE USE OF SUBLINGUAL NITROGLYCERIN PRIOR TO CORONARY ANGIOGRAPHY CORONARY ANGIOGRAPHIC EFFECTS OF NITROGLYCERIN ON PERCENT CORONARY LUMEN DIAMETER REDUCTION IN MAN

Nitroglycerin is commonly used in the angiographic laboratory in order to enhance visualization of coronary arteries. Often, angiograms are not performed prior to nitroglycerin administration. We initiated a study to determine whether or not the use of nitroglycerin affected the estimation of percent lumen diameter reduction in man.

(A) Study Design

We approached this problem in the following manner. Forty seven patients undergoing routine angiography had nitrates withheld for greater than 2 hours before angiography. Cine frames were matched to the same portion and part of the cardiac cycle pre nitroglycerin and post-nitroglycerin. The diameter of the projected coronary arteries and narrowings were measured with callipers to help reduce the error in interpretation. The percent coronary artery narrowing was determined by dividing the diameter of the narrowing by the vessel diameter immediately proximal to the narrowing and multiplying by 100.

(B) Results

Figure 13 shows the changes in coronary artery diameter following the administration of sublingual nitroglycerin. Each data point

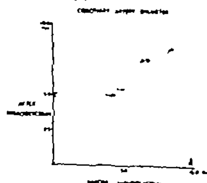


Figure 13 Changes in coronary artery diameter following the administration of sublingual nitroglycerin (see text)

rienced coronary angiographers without knowledge of the other s findings (8) Figure 8 illustrates the accuracy of our angiographic interpretation when compared to the true narrowing, (measured by coronary artery casts). The vertical axis is percent deviation from the true narrowing and the horizontal axis is the true percent diameter reduction. There was little error when 20 and 90 % nar rowings were estimated subjectively How ever in the arteries with 50 and 60 % lumen diameter reduction our error was much grea ter The error consistently over-estimated the degree of narrowing. The lower panel sum marizes the analysis of the same coronary arteries when measured with calipers. Once again the 20 and 90 % narrowings are close to the actual degree of narrowing whereas 50 and 60 % narrowings produced a higher de gree of deviation from the actual value.

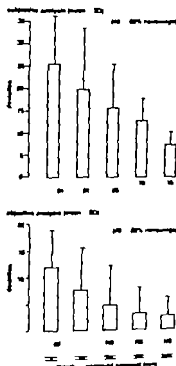


Figure 9 Accuracy of subjective and objective ana lysis of 40—60 % coronary artery nar rowings (see text)

Figure 9 illustrates the accuracy of subjec tive assessment (top panel) of 40—60 % nar rowings of varying length It is visually obvi ous that as the length of the narrowing in creases, the percent deviation from the true value decreases. Thus a 40—60 % narrowing of 1 mm in length was assessed least accura tely The lower panel is a similar analysis using calipers to measure the percent narrow ing. Clearly accuracy improves as length narrowing increases. We were most ate for 40—60 % narrowings of 1 mm length, regardless of the method used.

(B) Relationship of the Visual 4 Percent Coronary Narrowing True Narrowing and Measured Coronary Flow

Figure 10 is a left anterior oblique left ronary angiogram without hyperemic

CONTROL



Figure 10 Coronary angiogram without tion to illustrate resting coronary flow and blood flow after injection of a giographic contrast material

nary blood flow Figure 11 illustrates point about the visual over-estimation of c ronary artery narrowings. This cine fram represent a true 50 % narrowing, 1 mm lo

50% NARROWING

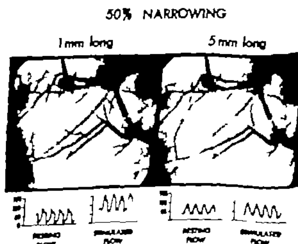
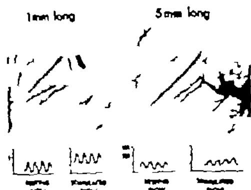


Figure 11 Coronary angiogram of a 50 % narrow ing 1 mm and 5 mm in length (see text)



12 Coronary angiogram of a 70% narrowing 1 mm and 5 mm in length (see text)

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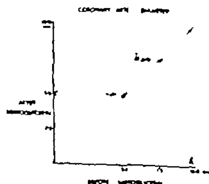


Figure 13 Changes in coronary artery diameter following the administration of sublingual nitroglycerin (see text)

represents a pre and post-operative coronary diameter Vessels that failed to increase in size following sublingual nitroglycerin fall on the line of identity Figure 14 shows the change in the diameter of the narrowing. The data illustrate that the majority of coronary artery narrowings do not change diameter

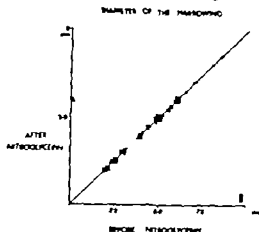


Figure 14 Changes in the diameter of the coronary narrowing following the administration of sublingual nitroglycerin (see text)

following nitroglycerin administration However of those that did change diameter the majority increased in size. Figure 15 illustrates the change in percent coronary narrowing after nitroglycerin administration Obviously the response is variable but the majority of patients increased the percent of coronary narrowing following nitroglycerin The shaded area, is of particular interest since *these data points represent vessels narrowed* less than 50 % prior to nitroglycerin. Following the administration of nitroglycerin the percent narrowing increased to greater than 50 %.

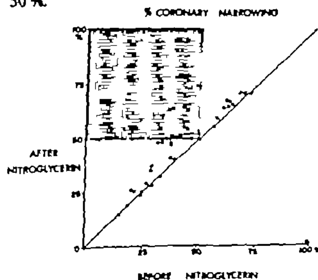


Figure 15 Change in percent coronary narrowing after sublingual nitroglycerin (see text)

(C) Conclusion

Our observations indicate that adm tration of sublingual nitroglycerin ι dilates the coronary artery *proximal to* narrowing, whereas coronary usually remain fixed after ni Therefore the percent narrowing usually creases. However this is not universally case and the variability of the response m be considered when evaluating the *narrowing of individual coronary* is obvious that nitroglycerin may influe the interpretation of coronary

IV SUMMARY

It is hazardous to rely solely on angiography to define critical coronary tery stenosis. The physiologic significance a narrowing observed at coronary angi phy can best be evaluated by the addition stress testing, i e. exercise or pacing tach cardia *with ECG monitoring*, as well as re ing and exercise isotope perfusion studie *However when evaluating coronary ang* grams for critical coronary artery st several points are worth considering. Fi long narrowing will decrease coronary bloo flow more than a short narrowing of the sa severity Second, sequential narrowings w decrease coronary blood *flow more tha* *single narrowing of the same total leng* Third, a long narrowing can be estimate *more accurately than a short narrowi* Fourth *caliper measurements of corona artery narrowings are more accurate th* subjective estimation. Fifth, coronary arte *dilators may increase the percentage narrow* ing in some cases.

The complex effects of percent stenos and length of stenosis on the physiology o coronary blood flow must always be consi dered when evaluating angiograms. In ad dition, the angiographic or photographic ar tefacts produced by short narrowings tend to over-estimate the percent stenosis and thu calipers should be used to measure percen stenosis especially in the short narrowings Finally nitroglycerin should not be used rou tinely prior to coronary angiogr

REFERENCES

1. GOULD K.L., LIPSCOMB K., HAMILTON G W Physiologic basis for assessing critical coronary steosis. Am J Cardiol. 33 87—94 1974
2. LAWRIE, D.J., LEVINSKY R.A., LEWIS R.M., THOMPSON H K., COLE, J.S. A mathematical model describing the effects of coronary artery stenosis on coronary blood flow in resting and stressed dogs. Cardiovas Res. Cent. Bull 13 52—60 1975
3. GOULD K.L., LIPSCOMB K. Effects of coronary stenosis on coronary flow reserve and resistance. Am. J Cardiol 34 48—55 1974
4. HILLIS W.S., FRIESINGER, G C. Reactive hyperemia an index of the significance of coronary stenoses. Am Heart J 92 737 1976.
5. FELDMAN R.L., NICHOLS W W., PEPINE, C.J What is the coronary hemodynamic significance of the length of a coronary artery obstruction? Clin. Res. 24 216A, 1976.
6. FOLTS, J D., GALLAGHER, K P., ROWE, G G Phasic coronary blood flow changes with partial coronary artery obstruction. Physiologist 17—223 1974
7. FURUSE, A., KLOPP E.H., BRAWLEY R.K., GOTT V L. Hemodynamic determinations in the assessment of distal coronary artery disease. J Surg. Res. 19 25—33 1975
8. PEPINE, C.J., FELDMAN R.L., NICHOLS W W., CONTI, C., R. Coronary angiography potentially serious sources of error in interpretation. Cardiovascular Medicine, 747—756, August 1977



3.

ORONARY ARTERIOGRAPHY—AN OBJECTIVE METHOD?

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Coronary arteriography is considered necess ary today for decisions on treatment and management of patients with coronary artery disease. The coronary arteriogram is in fact the basis on which most of these decisions are made. (1)

The purpose of performing coronary arte riography is to detect and grade coronary artery stenosis.

The value of coronary arteriography is based on the assumption that coronary artery flow is inversely related to the degree of ste nosis as we see them on the coronary arterio-grams. The further assumption is made that this flow is related to the nutrient flow or to the demands for nutrient and oxygen in the muscle in an area distal to the coronary artery stenosis. The visualization and evaluation of collaterals are based on the same assumption

Obviously these assumptions can be and have been questioned. Let us avoid this problem and assume that there is a relation ship between the flow in the coronary arteries and the stenosis as we see them on the coro-nary arteriogram

It is highly desirable that the coronary ar teriograms are technically satisfactory The chances of detecting and grading stenosis de creases with poor image quality

There is a quality program with coronary arteriography and suboptimal coronary arte riograms are performed every day Does this mean that some patients are not receiving adequate medical care because of poor quality coronary arteriograms? I would say no and suggest that this means that high quality coronary arteriography is *not* necess ary for good medical care of patients with coronary artery disease.

But this is not the problem to be discussed here and let us assume that all coronary arte riograms are of optimal quality

The next question will then be what is the optimal quality of coronary arteriograms? Most radiologists cardiologists and laymen prefer high contrast black and white arteri ography They do so regardless of the infor mation content of the arteriogram This is an interesting psychological phenomenon I am not qualified to go into that and I will just make a few remarks. One reason for prefer ring the high contrast black and white arterio-grams is that you can make excellent slides and illustrations from them

The psychological impact of the hig trast high resolution arteriogram is able and the emotional effect of it ha realized and used

I would like to submit that the higl trast arteriogram is not necessarily th arteriogram containing the most valual formation But this is again not the pr to be discussed, so let us assume that w the best coronary arteriograms availab

Then how do we assess our coronar riogram? We look at them and what angiographers do is to express a steno a percent reduction of the coronary compared to the pre-stenosis size of tl tery

All reports concerning treatment and nosis of coronary disease have tables li stenosis of the coronary arteries as 30 5 90 99 percent, etc.

Percent reduction of what cross sectional area or even circumf If you ask this question angi usually become puzzled and after a most will say that they mean reductio cross sectional area.

This answer implies that in fact, we h considerable subjective element in the as ment of coronary artery stenosis.

For what we can observe directly two-dimensional coronary arteriogram only the diameters in different segment the artery

If we are to arrive at a percentage reduc of cross sectional area after observing dia ters, we have to perform calculations that impossible for most individuals without aid of a calculator or pen and paper

This means that when angiographers talking about percent stenosis referring cross sectional area they are not very ob tive but using an impression, or if you wil gestalt approach to the problem In ot words, they have a "feeling" for what a 7 stenosis should look like.

The impression or interpretion of coron arteriograms varies also from individual individual and as travelling angiograph you can easily make the observation that 50 stenosis in Europe, for instance is not t same as 50 % of stenosis in the U S A

So we have circumstantial evidence th there are considerable subjective elements i assessing coronary artery stenosis.

o investigate this in more detail a study)s recently performed. (2) The purpose of study was twofold.

To study observer performance in assessing coronary artery stenosis.
Compare the diagnostic information on 16 mm cine film and 70 mm fluorography

..ODS

30 unselected patients with CAD
Judkin s technique for coronary arteriography
Both 16 mm cine and 70 mm camera recordings of 42 projections of left and 32 projections of right coronary artry
The same 7" cesium-iodide image intensifier and 0.6 mm focal spot tube for both recordings.
16 mm cine at 50 frames per second 70—100 Kv and 8 mR per frame.
70 mm films at 4 frames per second 70—100 Kv and 80 mR per frame.
Dose of contrast agent and rate of injection constant.
16 mm cine and 70 mm film viewed independently in random order by four trained observers without knowledge of the patient.
Each recording studied separately location of stenosis, degree of stenosis (% reduction in diameter) and presence of collateral circulation recorded.
Two months interval between viewing 16 mm cine and 70 mm films and between first and second viewing.
In addition 29 stenoses measured on 70 mm films within 0.1 mm

..JLTS

ere was no difference between these obser rs ability to detect stenosis when using 16 cine film and 70 mm films.

There was *considerable inter-observer dif* n estimating the degree of coronary ery stenosis (fig. 1). This was true for both mm cine and 70 mm film observations. In instances the observers estimates were d against the estimates of coronary ar ..al stenosis in the official report of the partment of radiology

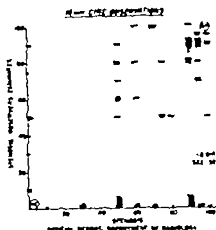


Fig 1 Comparison between estimates of coronary arterial stenosis in the official report and by four independent observers using 16 mm cine film Figures in circles indicate report-observer agreement on 0 percent stenosis (46) and on 100 percent stenosis (63). Similar results were obtained with 70 mm films

2. There were also *considerable intra-observer differences* in separate observations of 16 mm cine films and 70 mm films (fig. 2).
In 18 % of the cases the observers changed their estimate across the 50 % diameter stenosis line between the two observations.

3 There was nearly complete agreement regarding the presence and location of collerals with both 16 mm and 70 mm films.

INTRAOBSERVER DIFFERENCES ON 70mm FILMS

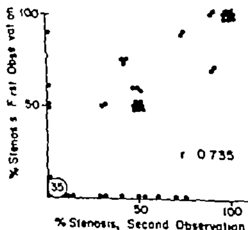


Fig 2 Intra-observer differences in separate observation on 70 mm films Each of the four observers reviewed the films twice with a 2 month interval between readings.

The following additional observations were made

a) Among the four observers no two agreed on a definitely erroneous interpretation

b) All observers had variations of estimates in both directions.

c) The widest variation between estimates were found with stenosis in LAD

d) Observer performance improved only little with longer experience.

e) Complete agreement as to the location of stenosis when recorded

One way to improve the accuracy of coronary arteriography assessment is to make measurements on the coronary arteriograms. Several investigators have tried this and expressed varying degrees of confidence in their results. Others have been critical about the possibilities of measuring small vessels in patients

Since there seems to be some confusion regarding the possibilities of actual measuring coronary artery size on cine films or 70 mm films some simple experiments were performed using plastic tubes as models for coronary arteries and the best imaging systems available at present. (3)

The same recording systems were used as in the study on observer performance The conditions for imaging were optimum and different from conditions present in patients in many respects. The degree of magnification could be calculated exactly The tubes were curved only in one place. The object did not move and the tube was constantly filled with undiluted contrast medium The angiographic measurements of cross sectional areas were compared with the true cross sectional areas of the stenosis on the tube. Generally the angiographic measurements were not very accurate (Fig. 3) As expected the incidence of the central beam had great influence on the accuracy of the measurements.

It appears that true measurements of coronary artery stenosis and of coronary arteries with diameters below 3 mm simply are not possible in patients even with the best recording systems commercialy available. This is not totally expected but it is important to emphasize this limitation of the present imaging systems. These findings partly explain the difficulty in estimating physiologic effects of anatomic lesions as they appear at coronary angiography

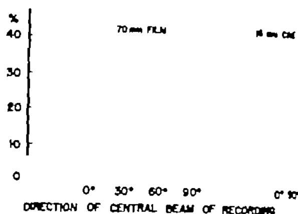


Fig 3 Accuracy of angiographic measurements stenosis of a plastic tube The deviation from the cross sectional area is given in percent

SUMMARY AND CONCLUSION

There is considerable inter and intr observer error in estimating coronary arte stenosis on coronary arteriograms

There is no obvious way to increase th accuracy of coronary arteriography

Measurements are of little or no value i arteries and structures below 3 mm in size.

Coronary arteriography is only a semiqu antitative method for making decisions on treatment prognosis and follow up of pa tients with coronary artery di

REFERENCES

1 DUNKMAN W., BRUCE, M.D., PER LOFF JOSEPH K., M D., F.A.C.P., KASTOR, JOHN A., M.D., F.A.C.P., and SHELBURNE, JAMES C., M.D., F.A.C.P Medical Perspectives in Coronary Artery Surgery—a Caveat. American Journal of Medicine 81 817 1974

2. BJöRK LARS M D., SPINDOLA FRANK, HUGO M.D., HOUTEN VAN FRANCIS X., M.D., COHN PETER F., M.D., and ADAMS, FACE DOUGLASS F., M.D Comparison of Observer Per formance with 16 mm Cinefluorography and 70 mm Camera Fluorography in Coronary Arteriography The American Journal of Cardiology 36 474 1975

3 BJöRK L., and O KEEFE, A. Esti mation of coronary artery stenosis. Limi tations of present methods. Acta Radiologica Diagnosis 17 777 1976.

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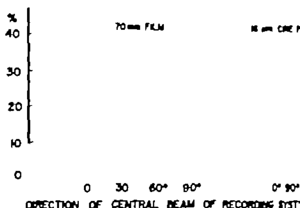


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4.

COMPUTER GENERATED INDEX FOR THE ASSESSMENT OF CORONARY ANGIOGRAPHY

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D.L. Stone,
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ulation of the index

$$Wi = 1 - \frac{Li}{4}$$

Wi is the weighting of the ith vessel
Li is the size of the lesion in the ith vessel and its value varies from 0 to 4 where

0 = No lesion
1 = 25 % lesion
2 = 50 % lesion
3 = 75 % lesion
4 = 100 % lesion

al coronary index is calculated according he formula

$$= \frac{100}{NTV}$$

1 [W2 + W2.W3 (W4 + W5) + W6 (W7 8 + W9)] + W10(W11 + W12 + W13)}

where NTV = number of terminal vessels.

nis system yields values for the indices ween 0 and 100 where 0 corresponds to obstruction and 100 to no obstruction

Retrograde filling as seen in the angiogram be incorporated into the model. 2 levels were applied, 50 % and 100 %. ... reduce the relevant lesions to half and o their original weighting respectively

Data used in this study originated from the gations of patients with suspected coary artery disease At present the data ık contains information on more than) patients

SULTS AND CONCLUSIONS:

grade

gina wa classified according to N HA a from 0 (no angina) to 4 (rest pain).

igure 2 shows the relationship of the in to angina grade. The average value of the ex for each of the grades of angina was culated and plotted. Good relationship ex for grades 0–3 low values of the index associated with high angina grades i.e. re severe angina.

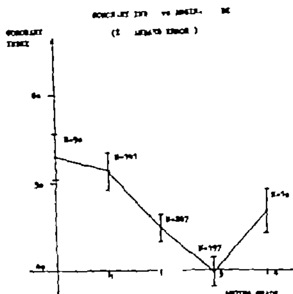


Figure 2

The mean value of the index rises for patients with rest pain.

Mean value of coronary index for patients with angina grade 1 or less was significantly different from the rest of the group The patients with grade 2, 3 and 4 angina had a lower average CI (42.4) compared with the grade 1 patients (51.5 p = 0 0001 n = 523).

In addition Fig. 3 shows that the shape of the curve is unaffected by 50 % or 100 % corrections for retrograde filling. The rise in index for patients with rest pain is probably explained by the heterogeneity of that group of patients which may even contain patients with normal coronary arteries or only minor disease.

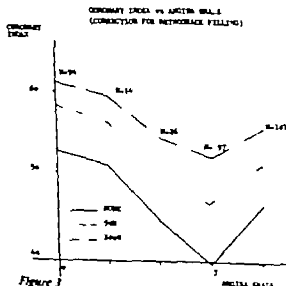


Figure 3

ABSTRACT

Mortality in patients with coronary artery disease is related to its severity The commonly used classification of 1 2 or 3 vessel disease is relatively insensitive We have designed a new classification which takes into account site severity and effect of multiple lesions in the coronary circulation Data is recorded on Mark Sense computer cards and a coronary index (CI) obtained We have collected data from 1100 patients and shown correlations of the index with clinical variables, ventricular function and in particular mortality

The prognosis of an individual patient with ischaemic heart disease is related to pathology documented by coronary arteriography Survival is a function of the number of vessels involved and the severity of the obstructions.[1 2,3] The natural history of patients with stable angina has been reported by several centres. [4–8] Those retrospective studies used varying criteria for selection and were performed before the introduction of bypass surgery In 1974 Reeves[9] published his analysis of existing data which suggested an annual mortality for single vessel disease was 2.2 %, for double 6 8 % and triple 11 4 %, with five year mortalities of approximately 17 %, 38 % and 55 % respectively These studies encompass the whole spectrum of ventricular function and this emerges as the second major factor in prediction of survival Several investigators have shown that with poor left ventricular function (abnormal haemodynamics reduced ejection fraction and wall motion abnormalities) five year survival is considerably reduced.[4,5] Aortocoronary bypass grafting relieves angina in 80–90 % of patients [11–15] There is some evidence to suggest it improves ventricular function [16,17] The controversy regarding its possible beneficial effect on life expectancy persists [31–33]

Many centres now have very low operative mortality (0 7–1 5 %)[23 24, 25] and impressive (93–98 %) three year survival curves, when compared with the natural history data [23–27] Patients are however selected and usually excluded with either diffuse coronary disease or poor left ventricular function Other reports suggest that survival is only improved in the patients with left main stem stenosis [18 20, 21 22] in particular the only randomised prospective study involving all groups of pa with coronary disease.[18] The high risk o left main stem lesion is related to its prox site prejudicing the blood supply to the left ventricular muscle. Friesinger et al also pointed out the importance of site st ing that survival of patients with lesions of anterior descending coronary artery pended upon whether it was proximal tal to the first septal branch. They also the severity of lesions from 0–5 We l developed a scoring system[29 30] that takes account the severity of lesions on a (scale their site, the effect of multiple lesi and possible effects of retrograde filling data is collected on computer Mark Se cards so that multiple methods of ana can be assessed.

METHODS

Definition of coronary index

The definition of the index is based o assumptions about the nature of the relati ship between the lesions in various branc of the coronary arteries and the magnit their overall effect.

1 Serial lesions multiply in effect.
2. Parallel lesions add in effect.
3 The effect of a lesion in any given v is directly proportional to the degree encroachment on arterial diameter

The proposed weighting system consists weights W1–W13 corresponding to vess V1–V13 (Fig. 1). The weights multiply add according to the positions of the lesio to form the final value of the index.

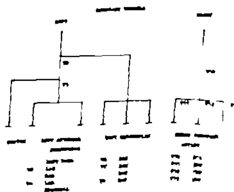
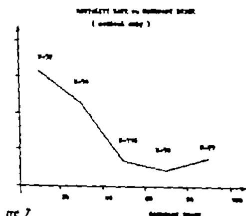


Figure 1

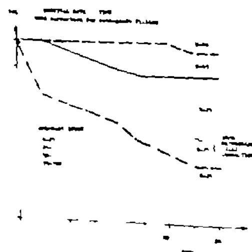
or all three of the vessel territories. The
of one second generation lesion
or without lesions in the third generation
u lity to 8 % per annum, and
or three second generation lesions to
ɫ (Fig. 6)

fortality correlates reasonably well with
Indices <20 are associated with high
lity rates (12–26 %) which fall with
asing coronary indices. (Fig. 7).



ire 7

ig. 8 shows the survival curves for the
rtiles of coronary index. The mortality for
ients with indices 50–100 is very low and
numbers small. With increasing severity
disease however survival becomes pro-
ssively worse. Correction for retrograde
ing has little affect on the survival curves
in particular does not improve the prog



nosis of patients with 0–50 indices with se
vere disease.

This method of analysis therefore seems to provide a reasonably sensitive means of defining high risk groups and potentially a method of comparing various forms of therapy

Exercise load

Exercise tolerance was assessed using bi cycle ergometry This was measured in increments of 150 kpm per minute starting at 150 kpm per minute Maximum achieved load was measured

Patients who achieved maximum exercise levels <450 kpm/min had a significantly lower CI than those able to reach higher work loads (42.3 cf 49 7 p = 0 0001 n=472) Fig. 4 Retrograde filling has been evaluated by assuming 50 or 100 % effectiveness. This only elevates the curves but does not change their shape suggesting that its presence does not affect exercise tolerance.

The group of patients unable to achieve 450 kpm/min during bicycle ergometry has a higher mean value of index than might be expected We think that this is due to the inability of certain patients to ride the bi cycle and who are therefore unable to do exercise properly It is important to note that the test was not a diagnostic exercise test, but one to assess maximal exercise capacity for follow up purposes and that angina was therefore not necessarily the end point of the investigation

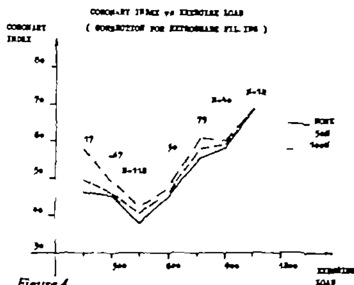


Figure 4

Left ventricular contraction

Figure 5 shows the relationship of the index to LV contraction when assessed by number of areas of akinesia or dyskinesia. Low values of the index are associated with more exten

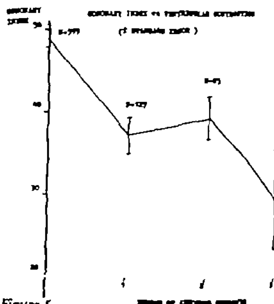


Figure 5

sive contraction abnormalities. If left ventricular contraction is defined as t or more areas of akinesia on the ang there is a significant difference between values of the index for normal and a ventricles (45.3 cf 39.2 P = 0 05 n = 802)

Mortality

The value of the index as an indicator prognosis will depend on its direct relat ship to mortality In this section only patients treated medically are considered

The site of severe lesions (grade 3 & 4) first evaluated in 297 patients treated cally and followed for up to two years. tients with third generation lesions i e. in terminal branches only had an annual mo ality rate of 2 % despite the fact that appro mately 40 % of these patients have lesions

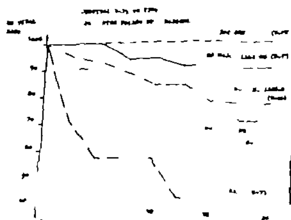


Figure 6

- se. J THOR. AND CARDIO-VASC SURGERY 70 405 1975
DUVOISIN G.E., LLOYD W.R., CANJI J.H., KENDALL, R.W Direct coronary artery surgery for prolonged survival in triple vessel coronary artery disease. CIRC. II 176 697 51—52, 1975
COHN L.H COLLINS J.J Improved long-term survival following coronary artery bypass. CIRC. III 166 655 49—50 1974
STILES Q.R., LINDESMITH G.G., TUCKER, B.L., HUGHES, R.K., KEYER, B.W Long term follow-up of patients with Coronary Artery Bypass grafts. CIRC. 54 6 III 32—34 1976.
KOUCHOUKOS N.T., OBERMAN A., KARP R.B RUSSELL, R.O Coronary bypass surgery Assessment of current operative risk. AM J CARDIOL 39 285 Feb 1977
FRIESINGER, G.C. 2nd International Symposium at Frankfurt. Feorg Thieme Verlag Stuttgart 1973
BALCON R. Correlation of angiographic findings and mortality in coronary artery disease Abstract at Paris meeting of British Cardiac Society B.H.J (In press).
STONE, D.L., FUERLIGHT J., CATTELL, M.R., BALCON R. A computer aided assessment of an index for scoring coronary angiogram. (Congress on computers in medicine) Rotterdam.
ROSS, R.S. Ischaemic Heart Disease An overview AM J CARDIOL 36 496 Oct. 1975
SELZERM A., COHN K. Asymptomatic Coronary Artery Disease and Coronary bypass surgery AM J CARDIOL 39 614 Apr 1977
PICHARD A. Coronary Arteriography for Everyone AM J CARDIOL 38 533 Oct. 1976.
LEACHMAN R.D Coronary Arteriography Selection of Patients. AM J CARDIOL 38 536 Oct. 1976
GULOTTA, S.J Coronary Arteriography 1976 — For whom? AM J CARDIOL 38 537 Oct. 1976

REFERENCES

1 HUMPHRIES J O KULLER L. ROSS R.S Natural history of ischaemic heart disease in relation to arteriographic findings CIRC 49 489—497 1974

2. FRIESINGER G C PAGE, E.E., ROSS R.S Prognostic significance of coronary arteriography TRANS ASSOC AM PHYSICIANS 83 78—92, 1970

3 BURGGRAF G N PARKER, J O Prognosis in coronary artery disease. CIRC 51 146—156 1975

4 BRUSCHKE A V G., PROUDFIT W L., SONES F M Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5 9 yrs. CIRC 47 1147—1153 1973

5 OBERMAN A., JONES W B RILEY C P Natural history of coronary artery disease. BULL, M Y., ACAD MED 48 1109—1125 1972.

6 MOBERG C H WEBSTER, J S SONES F M Natural history of severe proximal coronary disease as defined by cineangiography AM J CARDIOL 29 283 1972.

7 LICHTLEN P R. MOCCETTI T Prognostic aspects of coronary angiography CIRC 45 suppl 11 11—7 1972.

8 SLAGLE, R C BARTEL, A.G BEHAR V S Natural history of angiographically documented coronary artery disease CIRC 45 suppl 11 11—60 1972.

9 REEVES T.J., OBERMAN A JONES W B Natural history of angina pectoris. AM J CARDIOL 33 423—430 1974

10 FAVALORO R.G Saphenous vein auto graft replacement of severe segmental coronary artery occlusion ANN THORAC SURG 5 334 1968

11 MUNDTH E.D HARTHORNE, J N., BUCKLEY M.J., DAGGETT W M., AUSTEN W E. Direct coronary artery surgery for coronary artery occlusive disease AM J SURG 121 478 1971

12 MANLEY J C., JOHNSON W D Effects of surgery of angina and myocardial function CIRC 47—48 suppl III 162, 1972

13 KOUCHOUKOS N T KIRKLIN J W Coronary bypass operation for ischaemic heart disease. MOD CO CARDIOVASC. DIS 41 47 1972

14 ROSS D SUTTON R. SOWTON Venous graft surgery in treatment of coronary heart disease. BR. MED J 2 (1972.

15 BALCON R., RICKARDS, A WALSH W WILKINSON R.K. vestigation of patients with Angina selecton for aorto-coronary Vein Graft. Results of surgery BRIT 1972, 34 No 9 961

16 BOURASSA M G LESPERANCE CAMPEAU L., SALTIEL, J Fate left ventricular contraction follow aorto-coronary venous graft. CIRC 724 1972.

17 CHATTERJEE, K., SWAIN HJ PARMLEY W W Depression of ventricular function due to acute m cardial ischaemia and its reversal follo ing aorto-coronary saphenous vein pass. N ENGL. J MED 286 1117 1122, 1972.

18 TAKARO T HULTGREN H N TON M.J., DETRIE, K M The V co-operative randomised study of Sgery for Coronary Arterial Occlus Disease. II sub group with significant main lesions CIRC. 54 suppl III 1975

19 McCONAHAY D R., KILLEN D. McCALLISTER, B D., ARNOLD Coronary Artery Bypass Surgery for main coronary artery disease. AM CARDIOL. 37 885—889 1976

20 COHEN M V GORLIN R. Main Coronary Artery Disease. CIRC 275—285 1975

21 BANIM S O., DONALDSON R.M BALCON R Clinical Experience left main coronary artery stenosis. B H 38 1 71—76 1976

22. TALANO J V., SCANLON P MEADOWS W R. KAHN M Influence of Surgery on Survival in 145 patients with left main coronary artery disease. Suppl 1 to CIRC Vols. 51 and 5 1—105 1975

23 ULLYOT D.J., WISNESKI J., SULLIVAN R.W., GERTZ, E.W Improved survival after coronary artery surgery in patients with extensive coronary arter

disease. J THOR. AND CARDIO-VASC SURGERY 70 405 1975
DUVOISIN G E., LLOYD W R., CANJI J.H KENDALL, R.W Direct coronary artery surgery for prolonged survival in triple vessel coronary artery disease. CIRC. II 176.697 51—52, 1975
COHN L.H COLLINS J.J Improved long-term survival following coronary artery bypass. CIRC. III 166 655 49—50 1974
STILES, Q R., LINDESMITH, G G TUCKER, B.L., HUGHES, R.K., KEYER, B.W Long term follow-up of patients with Coronary Artery Bypass grafts. CIRC. 54 6 III 32—34 1976.
KOUCHOUKOS N T., OBERMAN A., KARP R.B., RUSSELL, R.O Coronary bypass surgery Assessment of current operative risk. AM. J CARDIOL. 39 285 Feb. 1977
FRIESINGER, G C. 2nd International Symposium at Frankfurt. Feorg Thieme Verlag Stuttgart 1973
BALCON R. Correlation of angiographic findings and mortality in coronary artery disease Abstract at Paris meeting of British Cardiac Society B H.J (In press).
STONE, D L., FUERLIGHT J CATTELL, M.R., BALCON R. A computer aided assessment of an index for scoring coronary angiogram. (Congress on computers in medicine) Rotterdam.
ROSS, R.S. Ischaemic Heart Disease An overview AM. J CARDIOL 36 496, Oct. 1975
SELZERM, A., COHN K. Asymptomatic Coronary Artery Disease and Coronary bypass surgery AM J CARDIOL 39 614 Apr 1977
PICHARD A. Coronary Arteriography for Everyone? AM. J CARDIOL. 38 533 Oct. 1976
LEACHMAN R.D Coronary Arteriography Selection of Patients. AM. J CARDIOL 38 536, Oct. 1976.
GULOTTA, S.J Coronary Arteriography 1976 — For whom? AM. J CARDIOL 38 537 Oct. 1976.

REFERENCES

1 HUMPHRIES J O., KULLER L ROSS R.S Natural history of ischaemic heart disease in relation to arteriographic findings. CIRC. 49 489—497 1974

2. FRIESINGER, G C PAGE E E. ROSS R.S Prognostic significance of coronary arteriography TRANS AS-SOC. AM PHYSICIANS 83 78—92, 1970

3 BURGGRAF G N., PARKER, J O Prognosis in coronary artery disease. CIRC 51 146—156 1975

4 BRUSCHKE, A.V G., PROUDFIT W L. SONES F M Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5 9 yrs CIRC 47 1147—1153 1973

5 OBERMAN A. JONES W B., RILEY C P Natural history of coronary artery disease *BULL, M Y., ACAD MED 48* 1109—1125 1972.

6 MOBERG C H., WEBSTER, J S SONES F M Natural history of severe proximal coronary disease as defined by cineangiography AM J CARDIOL 29 283 1972.

7 *LICHTLEN P R. MOCCETTI T* Prognostic aspects of coronary angiography CIRC 45 suppl 11 11—7 1972

8 SLAGLE, R.C., BARTEL, A.G BEHAR, V S Natural history of angiographically documented coronary artery disease. CIRC 45 suppl 11 11—60 1972

9 REEVES T.J OBERMAN A. JONES W B Natural history of angina pectoris. AM J CARDIOL 33 423—430 1974

10 FAVALORO R G Saphenous vein auto graft replacement of severe segmental coronary artery occlusion ANN THORAC SURG *5 334 1968*

11 MUNDTH E.D., HARTHORNE, J N BUCKLEY M.J., DAGGETT W M *AUSTEN W E. Direct coronary artery* surgery for coronary artery occlusive disease AM J SURG 121 478 1971

12 MANLEY J C JOHNSON W D Effects of surgery of angina and myocardial function CIRC 47—48 suppl III 162, 1972

13 KOUCHOUKOS N T., KIRKLIN J W Coronary bypass operation for ischaemic heart disease. MOD CO CARDIOVASC. DIS 41 47 1972

14 ROSS D SUTTON R., SOWTON Venous graft surgery in treatment of coronary heart disease BR. MED J 2 1972.

15 BALCON R., RICKARDS, A WALSH W., WILKINSON R.K vestigation of patients with Angina selecton for aorto-coronary Vein Bypass Graft. Results of surgery BRIT 1972, 34 No 9 961

16 BOURASSA, M G., LESPERANCE, CAMPEAU L., SALTIEL, J *left ventricular contraction following* aorto-coronary venous graft. CIRC. 724 1972.

17 CHATTERJEE, K. SWAIN HJ PARMLEY W W Depression of ventricular function due to acute myocardial ischaemia and its reversal following *aorto-coronary saphenous vein* bypass. N ENGL. J MED 286 1117—1122, 1972.

18 TAKARO T., HULTGREN H N TON M.J., DETRIE, K.M The co-operative randomised study of surgery for Coronary Arterial Occlusive *Disease. II sub group with significant* main lesions. CIRC 54 suppl III 1975

19 McCONAHAY D R., KILLEN D McCALLISTER, B D., ARNOLD Coronary Artery Bypass Surgery for main coronary artery disease. AM. *CARDIOL. 37 885—889 1976.*

20 COHEN M V., GORLIN R. Main Coronary Artery Disease. CIRC. *275—285 1975*

21 *BANIM S O., DONALDSON R.M* BALCON R Clinical Experience with *left main coronary artery stenosis.* B.H *38 1 71—76 1976*

22. TALANO J V., SCANLON P MEADOWS W R KAHN M Influence of Surgery on Survival in 145 patients with left main coronary artery disease Suppl 1 to CIRC Vols. 51 and 1—105 1975

23 ULLYOT D.J., WISNESKI J., SULLIVAN R.W., GERTZ, E.W Improved survival after coronary artery surgery patients with extensive coronary arte

disease. J THOR. AND CARDIO-VASC SURGERY 70 405 1975
DUVOISIN G.E., LLOYD W.R., CANJI J.H KENDALL, R.W Direct coronary artery surgery for prolonged survival in triple vessel coronary artery disease. CIRC. II 176. 697 51—52, 1975
COHN L.H COLLINS J.J Improved long-term survival following coronary artery bypass. CIRC. III 166 655 49—50 1974.
STILES, Q.R., LINDESMITH G.G., TUCKER, B.L., HUGHES, R.A., KEYER, B.W Long term follow up of patients with Coronary Artery Bypass grafts. CIRC. 54 6 III 32—34 1976
KOUCHOUKOS, N.T., OBERMAN A., KARP R.B RUSSELL, R.O Coronary bypass surgery Assessment of current operative risk. AM J CARDIOL. 39 285 Feb 1977
FRIESINGER, G.C. 2nd International Symposium at Frankfurt. Feorg Thieme Verlag Stuttgart 1973
BALCON R. Correlation of angiographic findings and mortality in coronary artery disease Abstract at Paris meeting of British Cardiac Society B.H.J (in press).
STONE, D.L., FUERLIGHT J., CATTELL, M.R., BALCON R. A computer aided assessment of an index for scoring coronary angiogram. (Congress on computers in medicine) Rotterdam
ROSS, R.S. Ischaemic Heart Disease An overview AM. J CARDIOL 36 496 Oct. 1975
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PICHARD A. Coronary Arteriography for Everyone? AM J CARDIOL. 38 533 Oct. 1976.
LEACHMAN R.D Coronary Arteriography Selection of Patients. AM J CARDIOL. 38 536 Oct. 1976.
GULOTTA, S.J Coronary Arteriography 1976 — For whom? AM J CARDIOL. 38 537 Oct. 1976.

REFERENCES

1 HUMPHRIES J O KULLER L., ROSS R.S Natural history of ischaemic heart disease in relation to arteriographic findings CIRC 49 489–497 1974
2 FRIESINGER G C PAGE, E.E., ROSS R.S Prognostic significance of coronary arteriography TRANS AS SOC. AM PHYSICIANS 83 78–92 1970
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6 MOBERG C H WEBSTER, J S SONES F M Natural history of severe proximal coronary disease as defined by cineangiography AM J CARDIOL 29 283 1972
7 LICHTLEN P R., MOCCETTI T Prognostic aspects of coronary angiography CIRC 45 suppl 11 11–7 1972.
8 SLAGLE, R.C BARTEL, A.G., BEHAR, V.S Natural history of angiographically documented coronary artery disease. CIRC 45 suppl 11 11–60 1972.
9 REEVES T.J., OBERMAN A., JONES W B Natural history of angina pectoris. AM J CARDIOL 33 423–430 1974
10 FAVALORO R.G Saphenous vein auto graft replacement of severe segmental coronary artery occlusion ANN THORAC SURG 5 334 1968
11 MUNDTH E.D., HARTHORNE, J N., BUCKLEY M.J., DAGGETT W M., AUSTEN W E. Direct coronary artery surgery for coronary artery occlusive disease AM J SURG 121 478 1971
12 MANLEY J C JOHNSON W D Effects of surgery of angina and myocardial function CIRC 47–48 suppl 111 162, 1972
13 KOUCHOUKOS N T KIRKLIN J W Coronary bypass operation for ischaemic heart disease. MOD CO CARDIOVASC DIS 41 47 1972.
14 ROSS D SUTTON R., SOWTO\ Venous graft surgery in treatment of coronary heart disease. BR. MED J 2 1972.
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16 BOURASSA, M G LESPERANCE CAMPEAU L., SALTIEL, J Fa left ventricular contraction for aorto-coronary venous graft. CIRC 724 1972.
17 CHATTERJEE, K., SWAIN H. PARMLEY W W Depression of l ventricular function due to acute m cardial ischaemia and its reversal foll. ing aorto-coronary saphenous vein pass. N ENGL. J MED 286 11 1122, 1972.
18 TAKARO T., HULTGREN H N TON M.J DETRIE, K M The co-operative randomised study of S gery for Coronary Arterial Occlus Disease. II sub group with significant main lesions. CIRC. 54 suppl. III 1975
19 McCONAHAY D R., KILLEN D McCALLISTER, B D., ARNOLD Coronary Artery Bypass Surgery for main coronary artery disease. AM. CARDIOL. 37 885–889 1976
20 COHEN M V GORLIN R. Main Coronary Artery Disease. CIRC 275–285 1975
21 BANIM S O., DONALDSON R. BALCON R. Clinical Experience w left main coronary artery stenosis. B.H. 38 1 71–76 1976
22. TALANO J V., SCANLON P.J MEADOWS W R., KAHN M In fluence of Surgery on Survival in 145 patients with left main coronary artery disease. Suppl. 1 to CIRC Vols. 51 and 5 1–105 1975
23 ULLYOT D.J WISNESKI J SULLIVAN R W., GERTZ. E.W Improved survival after coronary artery surgery in patients with extensive coronary artery

5.

SUDDEN OUT-OF HOSPITAL CORONARY DEATH AND CHRONIC LESIONS OF CORONARY ARTERIES AND MYO-CARDIUM MORPHOLOGIC DATA OF KAUNAS MALE POPULATION STUDY

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SUDDEN OUT-OF HOSPITAL CORONARY DEATH AND CHRONIC LESIONS OF CORONARY ARTERIES AND MYOCARDIUM
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Efforts to control coronary heart disease (CHD) in the population have a close re ationship to prevention of sudden death as more than half of CHD patients will die sud denly [1–8] In Kaunas, out-of hospital mortal ty due to acute CHD in 1969 accounted for 57 8 % of all fatal cases of definite and poss ble myocardial infarction (MI). Special ef forts to improve the organization of prehos pital medical care resulted in the decrease of out-of hospital mortality to 47 4 % (Table 1) n 1976 Owing to the lack of clear-cut man festations of cardiovascular disorders in around one fourth of CHD patients most of he deaths were unexpected occurring too rapidly for the persons to arrive at the hospi al before death [9–10]

According to current views the problem of prevention of sudden out-of hospital coronary death is closely related to the prevention and treatment of coronary atherosclerosis. Chronic obstruction of 75 % or more in one of the major subepicardial coronary arteries t least is noted by many observers in the majority of sudden death cases.[2, 11–19]

The fact that coronary atherosclerosis is a progressive disease which is manifest episodically[20] is confirmed by current angiogra phic studies of the natural history of coronary artery stenosis.[21] Anatomical characteristics of atherosclerotic changes in coronary arte ies and myocardium are to our mind of particular interest when obtained from the epresentative population contingent

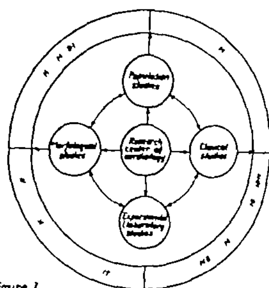


Figure 1

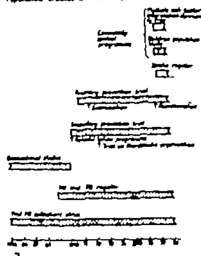
METHODS AND MATERIAL

In Kaunas Research Institute of Cardiolog extensive studies covering various aspects CHD control in the population are being ried out (Fig. 1). Population clinical, phologic, and experimental investigati are conducted making up an integrated tem permitting analysis of the various of healthy population, touching all the of the natural history of CHD All these in vestigations are performed in close ation with the existing health delivery sy — inpatient and outpatient medical ser and public health authorities.

Table I
Myocardial infarction register data for Kaunas

Year	Total of MI recorded	MI incidence per 1 000	Deaths			Mortality in hospital %	Death/percentage/total	Proportion of sudden in % of the total death
			Total	In hospital	Outside hospital			
970	328	1 06	154	44	110	19 8	46 9	71 4
971	388	1 27	160	44	116	16,2	41,2	72,5
972	427	1,39	188	66	122	21 6	44 0	64,9
973	447	1 46	177	74	103	20,5	39 6	58,2
974	489	1 45	193	76	117	19 6	39,5	60 6
975	476	[illegible]	[illegible]	77	91	18 9	35,3	54,2
976	501				82	20 4	34,5	[illegible]

nis paper presents some data on sudden y death cases accumulated in various of the population study (Fig. 2). Given covers the population group at hig risk, i.e., the male population of middle It is analysed in the following way the Kaunas male population aged 45—65 I then separately one of its segments %) representing the cohort of multifacto- CHD intervention study (this contingent been preliminarly examined and classi- l into risk groups). The study has started in z and the examined population was pro-



?

ctively followed up for five years.[22] MI ister[11] covering the whole Kaunas popu- without sex or age restrictions contri to the identification of sudden coro- death cases and their selection for cial morphologic study Cases of sudden of hospital coronary death were ident by using diagnostic follow up data, ilable medical records and findings of al morphologic investigations. A case of coronary death was considered as h when it had occurred within 6 hours of te onset of terminal event irrespective of ether there was a past history of CHD or t, and if a complete autopsy examination ruled out noncoronary causes of death. scope of the special morphologic study ong 127 cases of sudden out-of hospital death is shown in Table II

In all 127 cases, special morphologic inves- ations of major coronary arteries and myo- um were performed. In 88 cases, post angiograms were made. Right and

Table II
Incidence of Autopsies, Special Morphologic and Angiographic Investigations of Coronary Arteries and Myocardium in Cases of Sudden Coronary Death among Kaunas Male Population Aged 45—65

Scope of investigations	Whole male population (1970—1975)		Contingent of prospective epidemiologic study (1972—1977)	
	No.	%	No.	%
Total number of sudden coronary death	193	100	25	100
Autopsy performed	165	85,5	23	92
Autopsy and special morphologic investigation	127	65,3	22	88
Autopsy special morphologic investigation and angiography	88	45,6	11	44
Autopsy not performed	28	14,5	2	8

left coronary arteries were filled with barium gelatine mixture under a pressure of 120 mm Hg using Schlesinger apparatus for coronary injection. After angiography coronary arteries were examined by cross-sectioning at 1,5- to 2-mm intervals. The following points were determined the type of coronary artery distribution, location, degree, extension and character of obstructive lesions and the presence of collateral formations. Special instrument was used to determine the degree and extension of obstructive lesions. Obstructions of 50 % or more were taken into considerations. According to the extent, these obstructions were classified into short or local (less than 5 mm), tubular (5—15 mm), and diffuse (more than 15 mm or multiple local in the same segment). The mapping of all those pathologic changes were performed using the scheme recommended by the American Heart Association.[24] The chronic myocardial lesions were assessed by gross morphologic examination and histologic study of transverse slices of myocardium at intervals of 0,5—1 cm and by quantitative percentual evaluation of transmural scars.

RESULTS

Some clinical features obtained from the available medical records and diagnostic fol low up in the 127 cases are presented in Table III

Table III
Characterization of 127 Cases of Sudden Corona ry Death

History of Coronary Heart Disease	75 %
Hypertension	19 %
Diabetes mellitus	4 %
Length of terminal event less than 1 hour	46 %
Length of terminal event 1—6 hours	54 %
Average age of analysed cases	54 years

Chronic lesions of coronary arteries

Chronic obstructive lesions (atherosclerotic narrowing and old thrombotic occlusion) of 50 % or more have been found in all 127 cases. Those changes were present in at least one of four major coronary arteries (Table IV) In cases when significant obstruction was revealed in single or two arteries, luminal narrowing of lesser degree was found in other major coronary arteries as well in cases with luminal obstruction of 75 % or more, other arteries exhibited stenosis from 50 to 75 %, and in cases with narrowing of 50—75 % they exhibited 25 to 50 % resp Chronic obstruc tion of 50—75 % was found in 10 % of cases and as a rule, two three or all four major coronary arteries were affected Obstructive

Table IV
Number of Coronary Arteries with Chronic Ob struction in 127 Cases of Sudden Coronary Death

Number of affected arteries	Chronic obstruction (%)			
	50—75 %		75 % or more	
	No.	%	No	%
One	1	1	48 (14 §)	38 (29 §)
Two	5	4	49 (22 §)	39 (45 §)
Three	4	3	12 (8 §)	9 (67 §)
Four	3	2	5 (2 §)	4 (40 §)
Total	13	10	114 (46 §)	90 (36 §)

§ — with old thrombotic occlusion

lesions of 75 % or more were present in of cases, most often in two or one ma artery (39 % and 38 % resp.) and more in three or all four coronary arteries (13 Old thrombotic occlusions were present 36 % of examined cases. The greatest numb of old thrombotic occlusions was found two or three arteries were involved. In 3 ca organized thrombi were located in both fected arteries. Recent thrombi where most frequent finding in those cases w stenosis of 75 % or more occurred in sing two major coronary arteries. In 5 cases combined with old occlusions in other maj coronary arteries. On the whole, the left ant rior descending artery (Table V) was the mo frequent site of chronic obstructive lesions

Table V
Location of Chronic Obstruction of 50 % or Mo in Separate Coronary Arteries in 127 Cases Sudden Coronary Death

Affected artery		%
Left anterior descending	(LAD)	93 (9 §)
Right coronary artery	(RCA)	76 (21 §)
Left circumflex	(LC)	65 (7 §)
Left coronary artery	(LCA)	22 (1 §)

§ — with old thrombotic occlus

50 % or more, and the right coronary was more readily affected by old occlusions (21 %). When chronic obstruction both of 50—75 % and of 75 % or more, we present in two or three coronary arteries, most frequent combinations of involved arte ries were RCA LAD LAD-LC and RCA LAD-LC (Table VI). When a single arter was affected by obstruction of 75 % or more, it was RCA or LAD that was involved with equal frequency in such cases stenosis o lesser degree (50—75 %) also occurred in the other arteries in the same combinations men tioned above. Thus, the combinations of af fected arteries, taking into consideration the lesser degree of obstruction as well were identical in these cases too

Due to technical reasons angiograms of 76 cases only were analysed. In all 906 indivi dual segments of major coronary arteries were evaluated (Table VII). Chronic obstruc tion of 50 % or more was found in 325 (36 %)

VI
ıbination of Affected Coronary Arteries in Cases of Sudden Coronary Deth

ected Arteries Combination	Chronic Obstruction (%) 50–75 % No.	%	75 % or more No.	%
LCA	–	–	1	0,8
LAD	–	–	17	13,4
LC	1	0,8	9	7,2
RCA	–	–	21	16,6
RCA LAD	2	1,5	23	18 1
RCA LC	–	–	5	3 9
LAD-LC	2	1,5	19	15 0
LAD-LCA	1	0,8	2	1,5
RCA LAD-LC	3	2,3	10	8,0
LCA-RCA LAD	1	0,8	1	0,8
LCA-LC LAD	–	–	1	0,8
LCA LAD-LC RCA	3	2,3	5	3 9
al	13	10	114	90

them luminal narrowing of 50–75 % in ı (17 %), and that of 75 % or more in 172) of the evaluated segments. The most site of obstruction both of 50– and of 75 % or more, was found to be the ximal and middle segments of all three jor arteries and in the left main stem In *left* anterior descending and the right co- ary arteries atherosclerotic changes of tu ar and diffuse type (5 mm and more), of complicated by total occlusion, were the ant features In the left circumflex ar and the left main stem, short local (less n 5 mm) and tubular and diffuse (more n 5 mm) obstructions occurred with al the same frequency On the whole al two thirds of all revealed pathologic nges consisted of obstructive lesions of re than 5 mm In 36 cases of obstruction of or more and *in* 1 case of obstruction of 75 % intercoronary collateral filling was nd. It existed in almost all cases with 3 arteries, *in two thirds of cases when* d, and in one third of

Table VII
Incidence of Chronic Obstruction in the Individual Segments of Major Coronary Arteries in 76 Cases of Sudden Coronary Death (Postmortem Angiographic Data)

Individual segments of coronary arteries		Incidence of obstruction (stenosis occlusion) Number of evaluated segments No.	Number and % of found lesions No.	%	Chronic obstruction 50–75 % No	%	75 % or more No.	%
RCA	1	72	30	41	13	18	17	24
RCA	2	69	33	48	15	22	18	26
RCA	3	59	20	33	9	16	11	19
RCA	4	56	4	7	1	2	3	5
LCA	5	45	10	22	3	7	7	15
LAD	6	71	58	82	36	51	22	31
LAD	7	75	46	61	19	25	27	36
LAD	8	69	23	33	14	20	9	13
LAD	9	68	22	32	12	18	10	15
LAD	10	46	13	28	5	11	8	17
LC	11	76	25	33	14	18	11	14
LC	12	74	12	16	5	7	7	9
LC	13	73	20	27	5	7	15	20
LC	14	35	8	23	2	6	6	14
LC	15	18	1	5	–	–	1	5
Total		906	325	36	153	17	172	19

According to AHA

cases when a single artery was damaged. The right type of coronary artery distribution predominated.

Heart Weight

Heart weight was increased in most cases and in 85 % was over 400 g (Table VIII). There was no direct correlation between heart weight and the number of affected arteries and the length of terminal event. The increase in heart weight was more evident in cases when old transmural MI extended to 30 % or more and particularly in patients with hypertension.

Old myocardial infarctions (scars)

These were found in 87 cases (68 %) of sudden coronary death (Table IX). Old transmural MI was present in 52 cases (41 %) and nontransmural ones in 35 (27 %). Moreover

Table VIII
Characterization of Heart Weight in 127 Cases of Sudden Coronary Death (In connection with Length of Terminal Event)

Length of *terminal event*	400 g		400–499 g		500–599 g		>600 g		Total number	Average weight g
	No	%	No	%	No	%	No.	%		
1 hour	*3*	*5*	*25*	*42*	*16*	*27*	*15*	*26*	*59*	*511*
1–6 hours	16	24	28	41	18	26	6	9	68	*467*
Total	*19*	*15*	*53*	*42*	*34*	*27*	*21*	*16*	*127*	

in 5 cases of transmural scar and in 1 case of nontransmural scar they were paired Trans*mural infarction was found more frequently* in persons who had died within 1 hour than in those dying within 1–6 hours (51 % and 32 % resp) Anterior and anteroseptal and posterior and posteroseptal scars (transmural and nontransmural) were present with simi lar frequency There was a tendency for more frequent occurrence of old transmural poste*rior and posteroseptal infarction in persons* who died within 1 hour of the onset of termi nal event. Old infarction was found more often when more than one artery was affec ted. However when two three and four co*ronary arteries were involved, the frequency* of old infarction was similar (Table X).

COMMENT AND CONCLUSIONS

Chronic obstruction (atherosclerotic stenosis and old thrombotic occlusion) was present in 90 % of 127 examined cases of sudden nary death. Atherosclerotic stenosis of 5 *75—% was found in 10 % of cases old* botic occlusion in 36 %.

Predominantly (in 77 %) one or two ma coronary arteries had obstructive lesions 75 % or more. Chronic obstructive injury lesser degree (50–75 %) involved, as a r two three or all four major coronary arter However when single or two arteries e *bited severe obstruction other major* had luminal narrowing as well but of degree. When luminal narrowing rea *75 % or more, stenosis of other arteries* found to be of 50–75 % and in the cases w *narrowing of 50–75 %, 25–50 %* tively Old thrombotic occlusion took pl most frequently when two three or all fo major arteries were *involved* and was locat in the right coronary artery predominant The left anterior descending and right co nary arteries were the most common sites

Table IX
Characterization of frequency extension and location of old myocardial infarction and the length of terminal event in 127 cases of sudden coronary death

Length of terminal event	No of cases	Total No of MI	%	Transmural								*Not transmural*							
				Anterior and antero-septal		Posterior and postero-septal		Both anterior and posterior		Total		Anterior and antero-septal		Posterior and postero-septal		Both anterior and posterior		Total	
				No	%	No.	%	N o.	%	No.	%	No.	%	No.	%	N o.	%	No.	%
< hr	59	45	35	12	20	16	27	2	4	30	51	10	17	3	5	1	2	14	24
1–6 hr	68	42	33	8	12	11	16	3	4	22	32	9	13	12	18	–	–	21	31
Total	127	87	68	20	16	27	21	5	4	52	41	19	15	15	12	1	0.8	35	27

le X
...ationship between the Number of Affected Co... Arteries (Obstruction of 50% or More) and Frequency and Extension of Old Myocardial ...ction in 127 Cases of Sudden Coronary ...h

...of	No. of cases	Old myocardial infarction					
		Total		Trans-mural		Non-trans-mural	
		No.	%	No.	%	No	%
	49	28	57	14	29	14	29
	54	41	76	28	5	13	24
	24	18	75	10	42	8	33
	127	87	68	52	41	35	27

lesions (93 % and 77 % resp) such involving the proximal and middle of these arteries. Tubular and dif (length of 5 mm and more) types of ste ...s predominated. When chronic obstruc was simultaneously present in several arteries, mostly it was a combi of left anterior descending and right ...y arteries.

...oteworthy is the fact that in the cases of obstruction of 75 % or more in a ...gle artery it was mostly the right coronary left anterior descending arteries that were Such injury was usually accompa by stenosis of 50—75 % in the left ante r descending and circumflex branches and s made the same combination of affected arteries as in cases when two arte had luminal damage of 75 % or more. In ...w of the data suggesting that natural pro- ...on of stenotic coronary atherosclerosis predominantly in the proximal and ...ddle segments of left anterior descending d right coronary arteries,[n, n] the pre- injury in only one of them, must alert prospectively to the possibility of acute ...isodes of CHD In our opinion, obstruc ...n of 75 % or more in two coronary arteries most cases is apparently the triggering situ- in the development of transmural MI death.

The results of our study allow us to surmise sudden coronary death is an acute event the history of chronically advancing athe...rosclerotic heart disease. These data may appear helpful for the more precise definition of criteria for the selection of candidates for coronary artery surgery

ACKNOWLEDGEMENT

The authors are grateful to J Lubyte for help with data processing and technical assist ance.

SUMMARY

Some data on sudden coronary death path ology from CHD population study in Kaunas are presented. 127 cases of sudden out-of hospital coronary death were identified by means of diagnostic follow up data, avail able medical records and findings of special morphological investigations of coronary ar teries and myocardium. In 76 cases of them postmortem angiograms were made. Chronic obstruction (atherosclerotic stenosis and old thrombotic occlusion) was present in all cases, obstruction of 75 % and more forming the majority (90 %) of cases. Old thrombotic occlusion occurred in 36 %. Severe obstruc tive lesions (75 % or more) occurred predo- minantly in one or two arteries, while chronic obstruction of lesser degree (50—75 %) in volved as a rule two three or all four major arteries. Proximal and middle segments of the left anterior descending and right coronary arteries were the most common sites of chro- nic lesions. When chronic obstruction was simultaneously present in several coronary arteries, mostly it was a combination of left *anterior descending and right coronary arte- ries.*

In view of the data suggesting that natural progression of stenotic coronary atheroscle rosis occurs predominantly in proximal and middle segments of left anterior descending and right coronary arteries, the presence of injury in only one of them, must alert one prospectively to the possibility of acute epi- sodes of coronary heart disease.

REFERENCES

1 CHAZOV E.J., ELISEEV O M Prospects of developments and studies in cardiovascular diseases Cardiology (Moscow) *12* 10–15 1976

2 MAXUR, N.A ZHUKOV V N Sudden death of acute coronary insufficiency Cardiology (Moscow) *1* 27–31 1976

3 KANNEL, W B., DOYK J T Mc NAMARA, P M QUICKENTON P GORDON T Precursors of sudden coronary death Factors related to the incidence of sudden death. Circulation *51* 606–613 1975

4 OBERMAN A. RAY M TURNER, M E. BARNES G GROOMS C Sudden death in patients evaluated for ischemic heart disease. Circulation *52*, 6 suppl 3 111 170–111 175 1975

5 LOWN B Precoronary care and sudden death Clinician Sudden death, N Y 10–19 1975

6 JANUSHKEVICHIUS Z., BLOOZHAS J., JANKEVICHIUTE J et al In *Myocardial infarction community registers*, WHO Copenhagen 1976

7 JANUSHKEVICHIUS Z., BAUBINIENE, A., GRABAUSKAS V., DOMARKIENE, S., GLAZUNOV I Primary preventive study of coronary heart disease in Kaunas. CVD Epidemiology Newsletter *23* 27 1977

8 MILASHAUSKIENE M Registration of non hospital deaths due to acute myocardial infarction and its value for further development of medical care for coronary patients. CVD Epidemiology Newsletter *23* 27–28 1977

9 JANUSHKEVICHIUS Z., MILASHAUSKIENE M The recording of cases of non hospitalized patients sudden death due to acute myocardial infarction and acute coronary insufficiency and its importance for further improvement of the control of ischemic heart disease Cardiology (Moscow) *1* 22–26 1976

10 GORDON T., KANNEL, W B Premature mortality from coronary heart disease. The Framingham study JAMA 715 10 1617–1625 1971

11 JANUSHKEVICHIUS Z., BLO(OZ)HAS J., STALIORAITYTE, E., C(I)PONIS J., MAZHEIKA, L Clin morphologic characteristics of death —Materials of All Russian Co(n)gress of Cardiologists, 1977 In Print

12 STAMLER, J Primary prevention sudden coronary death. Circulation, 6 Suppl 3 111.258–111.279 1975.

13 PEVPER, J.A., KULLER, L.H., C(O)OPER M Arteriosclerosis of coron(ary) arteries in sudden unexpectd deaths. C(ir)culation *52*, 6 *Suppl. 3 111.27–111*. *1975*

14 MARGOLIS J R., HIRSHFELD J M D., NcNEER, J F., STARMER, C(F) ROSATI R.A., PETER, R.H., BEH(AR) V.S., KONG Y Sudden death due to coronary artery disease. A clinical hem(o)*dynamic and angiographic profile*. Ci(r)culation *52*, 6 Suppl 3 111 180 111 188 1975

15 BABA, N., BASHE, Jr WJ., KELLER M D GEER, J C ANTHONY JJ Pathology of atherosclerotic heart d(is)ease in sudden death I C *thrombosis and acute coronary vessel l(e)sions*. Circulation *52*, 6 Suppl. 111.53–111.59 1975

16 STAMLER J Sudden coronary dea(th) Approaches to its prevention. Sy(mpo)sium on cardiac rhythm disturbance *Medical Clinics of North America*, *60*, *245–282*, *1976*

17 REICHENBALD D D., MOSS N.S MEYER E. Pathology of the heart of sudden cardiac death. Amer J Cardio(l) *39* 865–872 1977

18 LIBERTSON R., NAGEL, EL HIRSCHMAN J C., NUSSENFE(LD) S R., BLACKBOURNE, M D DAVID J H *Pathophysiologic observations of prehospital ventricular fibrillation and sudden cardiac death* Circulation *4*(9) *790–798 1974*

19 LIE, J T., TITUS J L. Pathology of the *myocardium and the conduction system in sudden coronary death* Circulation *52 6 Suppl 3 111 41–111.52, 1975*

20 VLODAVER, Z., EDWARDS J E. *Pathology of coronary atherosclerosis*. Progr Cardiovasc. *Dis. 14* 256–274 1971

ROSCH J ANATONOVIC, R., TRE NOUTH R.S., RAHIMTOOLA, S.H., SIM D N DOTTER, C.T The natural history of coronary artery stenosis. A longitudinal angiographic assessment. Radiology *119* 3 513—520 1976

WHO-Kaunas-Rotterdam collaboration, Glasunov I.S. et al Janushkevichius, Z.I. et al., Burema L. et al. Behavioural and operational components of health intervention programmes project design. Chronic Diseases, WHO Copenhagen, 69—79 1973

Ischemic Heart Disease Registers. Report of the Fifth Working Group (including a second revision of the operating protocol) convened by the Regional Office for Europe of the World Health Organization. Copenhagen 26—27 April 1971 Copenhagen, 1971

AMA Committee Report. A reporting system on patients evaluated for coronary artery disease. Circulation *51* 773—808 1975

BEMIS, C.E., GORLING R., KEMP H.G et al. Progression of coronary artery disease. Circulation, *47* 455—464 1973

BURAKOVSKI V I RABOTNIKOV V.S. The role of myocardial revascularization in the treatment of ischaemic heart disease. Cardiology (Moscow), 6, 5—11 1977

6.

CORONARY ARTERIOGRAPHIC AND ELECTROCARDIOGRAPHIC CORRELATES OF SUDDEN CARDIAC DEATH

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While the mechanisms of sudden arrhythmic death are not clearly understood several studies from The Johns Hopkins University have recently implicated ischemia or infarction of the anteroseptal myocardial segment as important contributing factors in the genesis of ventricular fibrillation and tachycardia These findings will be summarized in this report

Sudden cardiac death or serious ventricular arrhythmias have been noted in several clinical situations including stable angina pectoris prolonged rest pain as a complication of acute myocardial infarction during exercise electrocardiography and the induction of anesthesia for bypass graft surgery The common arteriographic finding in most of these patients has been the presence of a 50 % or 70 % narrowing proximal to the origin of the first septal branch of the left anterior descending artery (LAD) either in the main left coronary artery (MLCA) or in the LAD segment proximal to this branch Patients with a proximal narrowing in either of these two coronary segments can often be identified by simultaneous electrocardiographic changes noted in leads I and/or AVL and V2 V5 at the time of angina pectoris or acute myocardial infarction

METHODS AND RESULTS

Stable angina pectoris[1]

During the eight year period between 1960 to 1967 350 patients underwent selective coronary arteriography at the Johns Hopkins Hospital Of this group 90 patients had at least one major coronary artery narrowed by 70 % or more a technically satisfactory arteriogram to permit complete interpretation and did not have primary valvular or myocardial disease. The coronary arteriograms of these 90 patients were reviewed in a "blinded" fashion without knowledge of the patient s subsequent clinical course and each patient was judged to "suitable" or "not suitable" for coronary artery bypass surgery by 1977 criteria Twelve patients were considered "not suitable" for bypass surgery (a) Nine were considered "non suitable" because of appreciable atherosclerotic plaque in the coronary segment distal to a significant narrowing at or beyond the usual bypass graft to coronary artery anastomotic site (b) three patients were considered to have severe ventricular dysfunction because the card thoracic ratio on the P A chest film was ter than 50 % *and* left ventricular end dia lic pressure was more than 20 mm Hg congestive left ventricular failure on clinical examination. Seventy-eight tients would be considered "suitable" for pass surgery by current criteria. No went any operative procedure. Long-term follow up for periods up to 12 years (9 8 yrs) is available for these 78 patien Fifty six of these 78 patients underwent double Master s exercise electrocard test at the time of coronary arteriography

Natural History Eight years after co arteriography 26 of the 68 patients with 70 % or greater narrowing in the LAD MLCA were dead compared to none of patients who did not have at least a 70 narrowing in either of these two vessels (P 0 05) Among the 68 patients, three had th 70 % or greater narrowing in the MLCA 65 had this narrowing in the LAD Pat with a 70 % or greater narrowing in eith LAD or MLCA were further analyzed basis of whether this narrowing occu proximal or distal to the first LAD sept perforating branch. The "distal" na was in the segment immediately beyond first septal branch (Fig. 1) Eight years a arteriography 21 (52 %) of the 40 pati with a significant narrowing proximal to first septal branch were dead while 6 (22 of the 28 patients with a narrowing distal the first septal branch were dead (P < 0.05

RISK OF DEATH AND LOCATION OF NARROWING IN LAD A

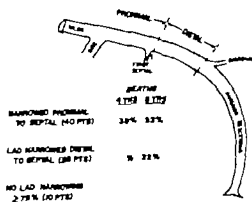


Figure 1

ise Electrocardiography The in on subsequent mortality of having a sitive or negative exercise electrocardio- could be analyzed for the 56 patients had this test at the time of coronary (Fig. 2) Mortality eight years arteriography was higher in those pa ts with a positive test compared with a tive test. ($P < 0.08$). The highest eight mortality was found in patients with a % or greater narrowing proximal to the t septal branch and a positive stress test. was no essential difference in eight mortality between those patients with a % or greater narrowing distal to the first branch (regardless of whether the test was positive or negative and patients with a 70 % or greater narrow proximal to the first septal branch but a ve stress test.

proximal LAD narrowing and a posi- exercise ECG test appears to identify the up at highest risk of subsequent death. If assumption is correct that "viable myo- m is required for a patient to have a ive stress ECG test, then the patient at risk of death would be the individual a proximal LAD narrowing and vi anteroseptal myocardium.

cardiac death Of the 78 patients suitable for bypass surgery by criteria, 31 have died of presumed diac causes up to 12 years after arteriogra The circumstances of death are known patients. Using a definition of sudden death as death occurring within one r of being ambulatory stable and well 15 ients died a sudden cardiac death and 14 not. (Table 1) Of the 20 patients who died had a 70 % or greater narrowing proximal to the first septal branch, 13 (65 %) died suddenly Of the nine patients who died and had a 70 % or greater narrowing in the distal LAD only two (22 %) died suddenly Thus 13 of 15 sudden cardiac death patients had a 70 % or greater narrowing proximal to the first septal branch of the LAD

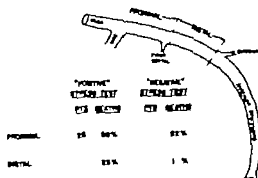


Figure 2

Arteriography in survivors of ventricular fibrillation or tachycardia[2]

One hundred and seventeen patients who recovered from either ventricular fibrillation (65 pts) or ventricular tachycardia (52 pts) subsequently underwent coronary arteriography at The Johns Hopkins Hospital between 1970–1977 All were found to have coronary heart disease defined as one major coronary artery narrowed by at least 50 %. In these patients, the ventricular dysrhythmia had occurred as a complication of an acute myocardial infarction (92 pts) prolonged angina pectoris requiring admission to a coronary care unit but without evidence of myocardial injury (11 pts) or during a treadmill exercise electrocardiogram (14 pts). The coronary arteriogra

e 1

ion of LAD narrowing and sudden cardiac death low-up to 12 yrs after coronary arteriography)

	N rrowing ≥ 70% Proximal to First LAD Septal Branch	Narrowing ≥ 70% in LAD Distal to First Septal Branch	No LAD Narrowing
ents	40	28	10
ent Deaths	20	9	2
den Cardiac Deaths	13 (65%)	(22)	0
Sudden Deaths	6 (30)	6 (50%)	2 (100%)
	1 (5%)	1 (11.)	0

phic fidings in these patients were reviewed as to whether (a) there was a 50 % or greater narrowing in one two or all three major coronary arteries (left anterior descending, left circumflex or right) In 13 patients a 50 % or greater narrowing in the MLCA was counted as at least two vessel disease (b) there was a 50 % or greater narrowing in the LAD segment proximal to the first septal branch or in the main left coronary artery

The extent of disease (single double or triple vessel disease) found in these 117 patients is shown in Table 2. Also included is whether there was a 50 % or greater narrowing in either the LAD or the MLCA, and whether the LAD narrowing was proximal to the first septal branch. Twenty two (85 %) of the 26 patients with single vessel disese had significant disease limited to the LAD In 18 (65 %) of these patients, the single significant narrowing was proximal to the first septal branch in four it was distal to the first septal branch but proximal to a second large septal branch Of the 117 patients 111 (95 %) had a 50 % or greater narrowing in either the LAD or MLCA, while 99 (85 %) had this narrowing proximal to the first LAD septal branch

Table 2
Location of > 50 % Narrowing in VF/VT

Extent of Disease	PTS	LAD or Main left	Proximal LAD or Main left
Single	26	22	18
Double	26	24	19
Triple	65	65	62
	117	111 (95%)	99 (85%)

There is no appreciable difference in the coronary arteriographic findings between patients that had ventricular fibrillation prior to

Table 3
Arteriographic Findings in VF/VT

Extent of Disease	VF	VT
Single	14 (22%)	12 (23%)
Double	15 (23%)	11 (21%)
Triple	36 (55%)	29 (56%)
	65	52

Table 4
Arteriographic Findings in VF/VT

	VF	VT	P
Patients (No.)	65	52	
SVD-LAD	10 (15%)	14 (26%)	N
LAD or MLCA Narrowed > 50%	60 (92%)	51 (98%)	
Proximal LAD or MLCA Narrowed > 50%	53 (81%)	45 (86%)	r

arteriography and those that had tachycardia. (Tables 3 and 4) The exten coronary disease (single, double and vessel) as well as the [illegible] with single vessel LAD disease, a 50 greater narrowing in the LAD or MLCA, those patients having this narrowing befc the first septal branch is not sigificantly ferent between these two patient groups.

Anesthesia for bypass graft surgery

Between 1969 and May 1973 269 underwent coronary artery bypass graft su gery at the Johns Hopkins Hospital. Ni (3 %) of these patients developed either tricular fibrillation or tachycardia during duction of anesthesia or prior to going cardiopulmonary bypass. Four of these tients had a 50 % or greater narrowing MLCA, four had a significant narro the LAD proximal to the first septal branc and one had a significant narrowing just di tal to the first septal branch but proximal t the second septal branch.

Survival after resuscitation of out-of hospit ventricular fibrillation

Cobb and his associates[4] have presented da on the two year mortality of 239 patients wh were initially resuscitated from out-of hospi tal ventricular fibrillation (Table 5). All pa tients were hospitalized and subsequen mortality after hospital discharge was exam ined by two criteria (a) whether the patien did or did not sustain a transmural infarctio identified by a new Q wave or (b) whethe the patient did or did not have myocardia "necrosis" defined as either a new Q wave or

f

[Survivors of Ventricular Fibrillation[49]

	Patients	Deaths (2 years)
Q Wave	39	5 (13%)
Q Wave	200	76 (38%)
al Necrosis	78	16 (20%)
Myocardial Necrosis	97	46 (47%)

w Q wave and Alfa 1 LDH > Alfa 2 LDH

of α 1 LDH that was greater ι 2 LDH Seventy-one percent of patients who died during the two-year ow-up period died suddenly When sub- mortality during the two years after Initial cardiac arrest was examined by ~ two criteria, significantly higher mort y was found in the group of patients who not develop a new Q wave or did not have of myocardial necrosis compared to patients who did develop a new Q wave or e evidence of myocardial necrosis. (P <). Among the patients who died, and the nstances of death are known, the major 53/75 71 %) were unexpected and occur outside of hospital.

authors strongly suggest that a patient tated from ventricular fibrillation evidence of an acute transmural in ction or myocardial necrosis is prone to urrent risk of sudden death, most likely ventricular fibrillation. Conversely myo- infarction at the time of ventricular fi- llation may convey some protection subsequent ventricular fibrillation. ι in these patients appears to associated with increased electrical ability

Electrocardiographic recognition of significant left anterior descending narrowing[1]

The twelve-lead electrocardiograms at the time of acute myocardial infarction (73 pts) or angina pectoris (33 pts) were examined in 106 patients with single vessel coronary ar tery disease. Single vessel disease was defined as one major coronary artery (left anterior descending, circumflex or right) narrowed by 70 % or more while other arteries were narrowed by less than 40 %. In the patients with acute infarction, only the appearance of new Q waves or ST segment shift of one millimeter or more (elevation or depression) or both, were noted. In those patients where the ECG was recorded during an episode of angina pectoris (either spontaneous or exercise induced), only reversible ST segment shift or T wave inversion or both were noted.

The ECG leads that showed new changes during infarction or reversible changes dur ing angina are recorded in Table 6. If signifi cant coronary disease is limited to one artery (e.g., the LAD), the changes will be found in the same leads whether the ECG is recorded during infarction or angina. No single ECG lead identifies disease in a specific vessel the myocardial segment perfused by the left an terior descending is reflected as a combination of leads I AVL and V1 – V5 the myocardium perfused by the right coronary ar tery is reflected in leads II III and AVF and the circumflex in leads II III AVF and V5 – V6. All patients with circumflex disease had ECG changes in at least two of the three inferior leads (II III, AVF) and there of ten also had changes in V5 or V6. Hence, if one examines the pattern or combination of ECG leads that are abnormal, it is usually possible to predict whether there is a signifi

ıe 6

c Changes in Single Vessel Disease

	PTS	No Patients with ECG Change in each lead											
		I	AVL	V_1	V_2	V_3	V_4	V_5	V_6	II	III	AVF
D	60	26	41	44	49	44	4	34	24	1	2	1
A	36	0	1	0	2	1	1	4	5	25	33	28
C	11	0	0	0	2	1	1	4	5	10	11	10

rd Q + /or ST shift Angina ST shift + /or T wave Inversion.

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ble 6
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	PTS	No. Patients with ECG Change in each lead											
		I	AVL	V_1	V_2	V_3	V_4	V_5	V_6	II	III	AVF
D	60	26	41	44	49	44	42	34	24	1	2	1
	36	0	1	0	2	1	1	4	5	25	33	28
C	11	0	0	0	2	1	1	4	5	10	11	10

Q+/or ST shift Angina ST shift +/or T wave inversion.

cant narrowing in the left anterior descending artery

Often it is also possible to predict by electrocardiographic changes whether the significant LAD narrowing is proximal to both the first diagonal and first septal branches. Based on other data, Griffith[3] has proposed that the myocardium perfused by the first diagonal branch of the LAD is reflected in leads I and/or AVL and probably also V2—V3 while the myocardial segment perfused by the distal main stem is reflected in leads V2—V6 (Fig. 3) The patient who has simultaneous ECG changes in leads 1 and/or AVL and V2—V6 has myocardial ischemia or infarct in the myocardial segments perfused by the main stem LAD *and* the first LAD diagonal branch *Simultaneous ischemia or infarction* in both of these segments is usually due to a narrowing of the LAD proximal to or at the origin of the first LAD diagonal branch In more than 90% of patients the first LAD diagonal branch comes off the LAD proximal to or at the same level as the first septal branch For this reason

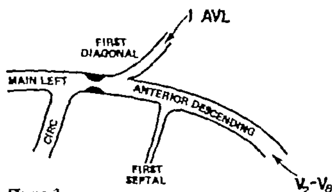


Figure 3

a narrowing proximal to the origin of the LAD diagonal branch is also proximal to the first septal branch Hence ECG changes in I and/or AVL *and* V2—V5 usually identify the patient with a significant narrowing in the *LAD proximal to the origin of both the first* diagonal branch *and* the first septal branch It should be noted that the magnitude of ECG changes in leads I and/or AVL is often less impressive than those found in the precordial leads (V2—V6)

All 73 patients with an acute anterior myocardial infarction complicated by ventricular fibrillation or tachycardia had changes in leads I and/or AVL as well as the precordial leads An example of these ECG changes is shown in Figure 4 This ECG was recorded at the time of CCU admission because o acute anterior infarction No significa tricular arrhythmias occurred at the initial hospitalization However on day this 62 year old male had a second p longed episode of chest pain and deve ventricular tachycardia at that time Co

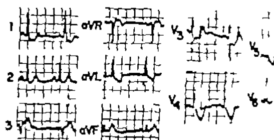


Figure 4

nary arteriography on the 12th hospital showed a 90% occlusion in the LAD mal to the origin of both the first and first septal branches.

DISCUSSION

The presence of a significant coronary ar narrowing in the main left coronary artery in the left anterior descending segment prox mal to the first septal branch appears to *a patient at "high risk" of subsequent death* serious ventricular dysrhythmia The data suggest this relationship have been from several clinical situations including tients with stable angina pectoris and longed rest angina as well as a complicat of acute infarction exercise electrocardi*ography and induction of anesthesia* for by pass graft surgery Taylor and his associ at Johns Hopkins have shown a similar cor relation between increased mortality follow ing survival from acute infarction and a 50 or greater narrowing proximal to the firs LAD septal branch compared to other pa tients who survived infarction but did not have a significant narrowing before the firs septal branch *All of these postinfarction pa tients studied by Taylor et al lived at least 1l* days after an acute infarction underwent re*search coronary arteriography prior to hos*pital discharge and were followed prospec*tively on only medical therapy*

There are at least two possible reasons why a proximal LAD narrowing might place a *patient at high risk of ventricular f* or tachycardia. *One explanation is*

myocardial segment in jeopardy of ische
; or infarction as a result of this proximal
D narrowing A narrowing in this location
l usually impair perfusion to three myo-
dial segments namely the myocardium
fused by the LAD diagonal the main stem
tal LAD and the interventricular septum.
second explanation relates to ischemia or
arction of the interventricular septum per
and the His-Purkinje system that is inclu
d in this segment.

The role that viable" myocardium has in
; genesis of ventricular fibrillation or ta
ycardia is yet to be determined. In the na-
al history study cited previously the pa
nts at highest risk of death (including sud
n cardiac death) appear to be those with a
gative stress ECG and a proximal LAD
rrowing. In a group of patients with single
sel coronary disease, Griffith[7] has sugges-
l that a positive' stress test identifies "vi
le myocardium in the distribution of the
structed coronary artery while a negative
ess test probably correlates with scarred"
yocardium in the distribution of the ob-
cted artery In the patients with single
sel disease, 'viability" or "scarring" of the
gment perfused by the obstructed coronary
ery had been identified by either retained
absent (akinesia) wall motion on left ven
culography Certainly Cobb s data on sur
al after resuscitation of out-of-hospital
ntricular fibrillation would suggest that the
k of a second episode of ventricular fibril
ion or death was significantly higher in
tients who did not have a transmural in-
rction or myocardial necrosis at the time
the initial cardiac arrest. Continued myo-
rdial viability" as contrasted with myo-
rdial scarring identified the patient at
gh risk of subsequent death.

If further prospective studies show a signi
ant narrowing proximal to the left anterior
scending first septal branch correlates with
high risk of death, especially sudden car
ac death, then appropriate non-invasive
ts to identify these patients must be devel-
ed. The use of Thallium-201 myocardial
rfusion imaging or recognition of simulta
ous ECG changes in I and/or AVL *and*
—V6 may prove useful Finally therape
ic regimens including specific anti-
rhythmic therapy or coronary artery bypass
rgery must be evaluated in patients whose
coronary artery and left ventricular anatomy
would place them at "high risk" of sudden
cardiac death

REFERENCES

1 PLATIA E.V., GRIFFITH L.S C and HUMPHRIES J O Location and severity of coronary artery narrowings as predictors of survival Circulation 52 (Supp IV) 11—91 1975 (abst.)

2 ANGELL, C S., and GRIFFITH L.S C Anteroseptal myocardial ischemia as a cause of ventricular fibrillation or tachycardia. Circulation 54 (Supp II) II—173 1976 (abst.)

3 GRIFFITH L.S C Unpublished data

4 COBB L.A., BAUMS R.S., ALVAREZ, H (III) SCHAFFER, W.A. Resuscitation from out of hospital ventricular fibrillation 4 years follow up American Heart Association Symposium on Sudden Coronary Death Outside Hospital Minneapolis October 10—12, 1974

5 GRIFFITH L.S.C. GRUNWALD L., ACHUFF S.C. Electrocardiographic changes in single vessel coronary disease. (Submitted for presentation at American College of Cardiology Annual Session Anaheim March 6—9 1978 (abst.)

6 TAYLOR, G HUMPHRIES J O GRIFFITH L.S C ACHUFF S.C. DUCCI H SCHULZE R. and PITT B Prognosis after acute infarction A function of angiographically identified myocardial risk segments. (To be presented at the 50th Scientific Session of the American Heart Association November 28—December 1 1977 Miami Beach, Florida.) (abst.)

7 GRIFFITH L.S C BAILEY I STRAUSS H W and PITT B Significance of segmental myocardial wall motion in the development of angina pectoris. Circulation 54 (Supp II) 11—6 1976 (abst.)

7.

HE EXERCISE ECG AND RELATED PHYSIOLOGICAL DATA ıS MARKERS OF CRITICAL CORONARY ARTERY LESIONS

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James M. Atkins,
John V Nixon,
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James T Willerson with technical assistance from
William E. Moore and
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From the Weinberger Laboratory for Cardiopulmonary Research, Moss Heart Center Department of Internal Medicine, The University of Texas Health Science Center at Dallas, Southwestern Medical School

Supported by Grants from NIHL (HLI 17669 and 06296) NASA (NGR 9026) and the Moss Heart Fund

The single most important determinant of the prognosis in acute myocardial infarction is the relative magnitude of muscle loss, i e. the ratio between the mass of the irreversibly damaged and the total left ventricular myocardial muscle mass (1) The prognosis in chronic ischemic heart disease may also be determined by the percentage of left ventricular mass that has been lost or is at high risk of sustaining ischemic injury Recent studies by Kalbfleisch and Hort (2) indicate that the left main coronary artery normally supplies nearly two-thirds (64 %) of the left ventricular muscle mass and the left anterior descending artery about 40 % (Table 1) These anatomical data are in agreement with the current clinical view that patients with left main or proximal anterior descending lesions join patients

Table 1
Relative Size of the left Ventricular Arterial Supply Areas
Per cent of total left ventricular myocardium supplied by the left anterior descending (LAD) circumflex (LCX) and right coronary (RCA) arteries

		Per cent supplied by		
Arterial pattern	N	LAD	LCX	RCA
Left	19	44	40	16
Balanced	129	42	21	37
Right	23	39	15	46
Total	171	42	22	36

From Kalbfleisch and Hort (1977)

with three vessel disease in a group of unfavorable prognosis (3)

We have explored the extent to which the sub-groups with poor prognosis may be identified by data derived from routine clinical exercise test. We asked the following specific questions

1 To what extent does the exercise ECG provide specific information on the localization of arterial lesions?
2. Can the combined electrocardiographic and physiological exercise test data identify patients with three vessel, left main or proximal left anterior descending artery disease?

MATERIAL AND METHODS

Several subsets of patients were exam[illegible] All had in common a history of chest [illegible] Patients with congenital valvular or myocardial disease were excluded as [illegible] patients with recent (less than two mon[illegible]) myocardial infarction Left ventricular [illegible] coronary cineangiograms were obtained [illegible] standard techniques (Sones or Judkins).

The exercise test was uniformly [illegible] continuous upright bicycle exercise [illegible] three minute work periods of progress[illegible] heavier loads. The test was carried to a sy[illegible] tom limited maximal level (4). Reasons [illegible] discontinuing exercise included silent bu[illegible] equivocally abnormal ST segment disp[illegible]ment. Peak work load was measured in [illegible] pondmeters per minute (kpm/min). O₂ uptake was estimated by the method of S[illegible]dell as modified by Sanne (5 6) related [illegible] age and sex specific standards (7) and [illegible]pressed as per cent of expected normal [illegible] values Indirect arterial pressures were rec[illegible]ded by a semi automatic device ([illegible] sphygmomanometer Narco Systems, In[illegible] and respiratory rate by a nasal thermistor.

The ECG analysis was based on a modi[illegible] Frank lead system Amplitude measurements were referred to the level of the PR se[illegible] immediately before the onset of QRS. S[illegible] amplitudes (Fig. 1) were measured at n[illegible] points defining eight subsegments of eq[illegible]

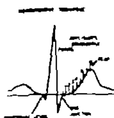
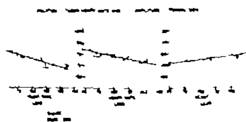


Fig 1 ECG Measurement Technique
ST is characterised by amplitude measurement [illegible] Frank leads X Y and Z at nine points dividing [illegible] interval End of QRS—Peak spatial magnitude of [illegible] into eight subsegments of equal duration The zer[illegible] reference level is the level of the P R segment imme[illegible]diately before the onset of QRS

duration between the end of QRS and peak T [illegible] ST2 distributions, i e. amplitudes at one fourth the distance between end of QRS and peak T were studied in detail The ECG methods including computer programs for wave recognition averaging, and measure[illegible]

ent have been fully described elsewhere (8

Normal reference data were obtained from group of 110 subjects, 65 men and 45 men, 18 to 29 years old. The normal data cluded bi-variate frontal and horizontal ane distributions in a subgroup of 40 men d women (9). Analysis of the normal ECG ta (Fig. 2) indicated that heart rate is a ajor determinant of the normal ST amplide (10). Linear correlation coefficients for d X (left to right) and Y (inferior superior) nge from 0.69 at the QRS-ST junction to 4 at ST 4 i.e. at the half way mark between end of QRS and peak T The heart rate rrelations were weaker in lead Z (poste



2. *Relation between Frank lead X Y and Z ST plitudes and heart rate during exercise in normal n*

r anterior). The strength of the orthogonal ds is lower than that of the standard chest ds. An ST amplitude of 3/4 mm in lead X the equivalent of 1 mm in V_5 (11). The rmal range in leads X and Y at maximal rt rates is 0.5 to 0.7 mm in men. Anterior displacement (corresponding to ST ele ion in leads V $_2$) up to 1.5 mm is a normal ding while any posterior displacement is normal.

There were significant sex differences with pect to the normal ST response to exercise g. 3). Women had more prominent super ST displacement than men i.e. larger ST ression in lead Y with a lower limit of 1 2 This difference may account for the high e of false positive ECG responses in men when conventional uniform criteria applied.

SULTS

e validity of the normal reference data for ECG analysis was tested in a series of 20 tients (mean age 47) with normal coronary eries, normal left ventricular catheteri

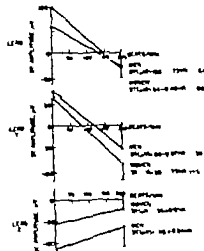


Fig 3 Relation between ST 2 amplitude and heart rate in normal men and women. Linear regression.

zation data, and on no digitalis. One of the twenty exceeded the lead heart rate sex specific limits as defined by the 5th and 95th percentile of the ST distributions in the young normal reference population

The relation between the extent of coronary artery disease and the characteristics of the ST segment during exercise was investi gated in a series of 67 patients with at least one 50 % diameter reduction in a major vessel A summary of the basic clinical data appears in Table II

Table II
ECG Series — General Characteristics
Extent of Coronary Artery Disease

	1 Vessel	2 Vessels	3 Vessels	Left Main	Total
No of patients	24	20	16	7	67
Per cent	36	30	24	10	100

Age Mean age 50.5±1.2 years, Range 32 to 67
Distribution of Single Vessel Disease
LAD 13 LCX 4, and RCA 7 patients.

I Effect of the site of coronary artery lesions on the spatial characteristics of the ST segment during exercise

The basic relationship between the site of arterial lesions and the ST segment characteris-

The single most important determinant of the prognosis in acute myocardial infarction is the relative magnitude of muscle loss i e. the ratio between the mass of the irreversibly damaged and the total left ventricular myo cardial muscle mass (1). The prognosis in chronic ischemic heart disease may also be determined by the percentage of left ventri cular mass that has been lost or is at high risk of sustaining ischemic injury Recent studies by Kalbfleisch and Hort (2) indicate that the left main coronary artery normally supplies nearly two thirds (64 %) of the left ventricular muscle mass and the left anterior descending artery about 40 % (Table I) These anatomical data are in agreement with the current clini cal view that patients with left main or proxi mal anterior descending lesions join patients

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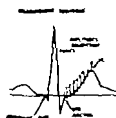


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positive electrode, the normal and the hemic myocardium. Transmural anterior d/or subendocardial posterior ischemia ll produce anterior ST displacement, i.e. elevation in standard leads V_{1-2}, while asmural posterior and/or subendocardial terior ischemia will result in posterior dis- cement. Furthermore, it seems inevitable at localization of the ischemic zone will ry for any given site of an arterial lesion th severity of the obstruction, presence or sence of collateral circulation and normal riations with respect to the geometry of the erial supply areas (2). The present series is all but nevertheless demonstrates that the fication of specific areas of ischemia in gle-vessel disease cannot be accurately edicted from the spatial characteristics of ST segment.

The extent of coronary disease as a deter- nant of ST segment characteristics

e relation between the extent of coronary ery disease and the prevalence of ST am tude abnormalities at rest and during ex cise is illustrated in Table III. The high rate ST abnormalities at rest among patients

ble III
valence of ST Abnormalities at Rest and du- g Exercise (Per Cent) Related to the Extent of ronary Artery Disease

	Diseased Vessels			
	1	2	3	Left main
st	12.0	10.5	62.5	28.5
ercise	76.0	79.0	93.8	83.5
	25	19	16	7

th three vessel disease is in agreement with evious findings (9). The increasing likeli od of abnormal ST response to exercise th increasing extent of coronary artery dis- se is well documented (12, 13, 21 – 23) in e literature (Fig. 6).

Lead by lead analysis of the relation be een heart rate and ST amplitude (Fig. 6) ealed no specific patterns. The average ak heart rate for patients with two and ree vessel disease was 129 beats per minute.



Fig. 6. Relation between the rate of abnormal ECG responses to exercise and the extent of coronary artery disease

Mean values were lower in left main disease (104 ± 5 beats per minute) and higher in single vessel disease (137 ± 5 bpm). The intra-group variations were large and the inter-group dif ferences were not statistically significant.

Evaluation of the spatial distribution of ST amplitudes during peak exercise (Fig. 7) de monstrated that 19 of 23 patients (83 %) with left main or three vessel disease had an ST vector during exercise located in the right upper anterior octant compared to 24 of 44 (55 %) of the patients with one or two vessel disease ($p < 0.01$ chi-square). The homogen ous distribution in three vessel and left main disease is consistent with widespread left ven- tricular subendocardial ischemia with an ST vector 180° away from the free wall. The more variable ST distributions in single and two vessel disease probably reflect the pre

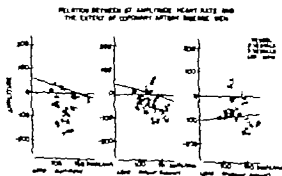


Fig. 7. Relation between Frank lead ST 2 ampli- tude, heart rate during exercise and the extent of coronary artery disease in 42 men. Dotted lines correspond to the 5th and 95th percentiles of the normal male ST distribution

tics was examined in a subgroup of 24 patients with single vessel disease The ECG response was abnormal in 13/14 patients with LAD lesions compared to 1/4 with circumflex and 5/7 with RCA lesions. The numbers are small but tend to support the findings by McHenry et al (12) who concluded that RCA and circumflex lesions frequently are electrocardiographically silent Others (13) have been unable to demonstrate any differences between subgroups of patients with single vessel disease.

There is little truly quantitative information on the spatial relationship between the anatomical site of the arterial lesion and the ST segment displacement. Most of the available spatial data deal with ST elevation, i.e. ST displacement to the left, inferiorly or anteriorly Exercise-induced ST elevation is a common feature during the early recovery stage after myocardial infarction (14 15). ST elevation is then usually found in leads with Q waves and is consistent with peri infarctional transmural ischemia. Old myocardial infarction associated with significant wall motion abnormalities is also found in a large number of patients with ST elevations during exercise in chronic coronary disease usually in the absence of angina pectoris (16). Data presented by Fortuin and Friesinger (17) suggest that exercise induced ST elevation also in the absence of previous myocardial infarction has a strong localizing power and usually is associated with a severe proximal stenosis of a major artery i e the anatomy of the classical Prinzmetal syndrome. Hegge et al (18) also compared electrocardiographic and angiographic data and found close agreement between the site of arterial lesions and the presence of ST elevation in anterior precordial leads Simoons (19) related the direction of the ST segment to the anatomical site of wall motion abnormalities and found a better correlation in inferior lesions. We have observed several patients with anterior ST displacement during exercise and severe proximal LAD obstructions (Fig. 4) but a critical analysis of our series of 24 patients with single vessel disease (Fig. 5) demonstrated that relationship between the site of the arterial lesion and the direction of the ST vector is complex

Significant leftward and/or inferior ST displacement (ST elevation in standard lateral or vertical leads) was seen in only patients and each had a remote transmu infarction and arterial lesions at the sites. The majority of the patients with LA lesions, or 9/13 had some degree of a displacement, but three patients had posterior displacement. Patients with RCA lesion were evenly divided between anterior posterior displacement.

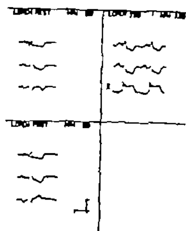


Fig 4 Transient ST elevation (anterior-right superior ST displacement) during exercise in a tient with a single vessel coronary disease i.e a 95 diameter reduction of the proximal left anterior scending artery Positive polarity lead X left Y in rior and Z anterior Calibration 200 msec/0.5 Load given as kpm/min

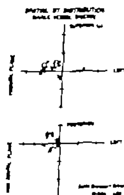


Fig 5 Spatial ST distribution in single vessel coronary disease
ST amplitudes measured at 2/8 the interval and QRS—peak T during symptom-limited maximal exercise N = 27

The overlap of ST sites in LAD and RCA lesions is not surprising. The injury current is generated in the boundary zone separating normal and ischemic myocardium (20) The direction of the ST segment displacement is determined by the spatial relation between

le V
ct of the Extent of Coronary Artery Disease and Beta Blockade on the Response to Exercise
an Values Standard Error

asurement	B-Block	No Disease	1 Vessel	2 Vessels	3 Vessels	Left Main
rt	–	148 6	142 6	134 10	1??±6	128 5
e	+	118 7	131 11	104 10	108 13	110 7
L	–	175 19	170 10	169 11	159±10	153 13
	+	170 10	172 9	150 10	153 19	145 11
P*		262 17	241 15	228 23	200 15	198 23
	+	206 22	227 25	158 24	182 25	157 14
2	–	62 4	54 3	60 3	50 4	52 6
	+	69 7	62 6	51 6	37 5	36 5
of	–	16	6	5	11	9
ients	+	19	10	7	15	5

Rate-pressure product (Heart Rate x Syst. Blood Pressure x 10^{-2}).
Peak oxygen uptake as per cent of normal age- and sex-specific mean values (7).

een subgroups with respect to age. Forty ree per cent of the patients with coronary sease and 44 % of the patients with normal ronary arteries were taking propranolol at e time of the study

As expected (27), hemodynamic and non vasive physiological data (Table V) demon rated a progressive functional impairment th increasing extent of coronary artery dis- se. Differences between patients with three ssel or left main disease and patients with rmal arteries with single vessel disease ere significant at least at the five per cent vel (t-test). Patients with left main and three ssel disease had similar exercise test data t three vessel disease was associated with ore prominent hemodynamic abnormal ies, including wall motion abnormalities (p 0.01).

All physiological measurements demon rated wide intra-group variations and con derable inter-group overlap No single data oint provided any separation of clinical va e.

Beta blocking agents tended to obliterate ter-group differences with respect to heart ate and rate pressure product (heart rate x ystolic blood pressure x 10^{-2}) but differences ith respect to peak work load and peak ox gen uptake persisted. Clinical consideration often necessitates evaluation of the patient during continued beta-adrenergic blockade.

We therefore selected work load as an index of cardiovascular functional capacity Use of estimated oxygen uptake normalized for body weight proved ineffective in our population since no less than 85 % of the female and 60 % of the male patients were classified as grossly overweight by their ponderal indices.

The combined requirement of signs of ischemia during the exercise test, i.e. ST segment abnormality and/or typical angina pectoris, and a low work capacity i.e. peak work load 400 kpm/min in men and 250 kpm/min. in women had considerable dis-

Table VI
Identification of Patients with 3 Vessel and Left Main Disease

Criteria for Positive Test Angina and/or ST Abnormality at Low Work Load (≤ 400 kpm/min. in men and ≤ 250 in women)

		No of Patients with		
		0- Vessel	3 Vessel	Left Main
Ischemia at Low Work Load	+	4	12	11
	–	65	14	3
Total		69	26	14

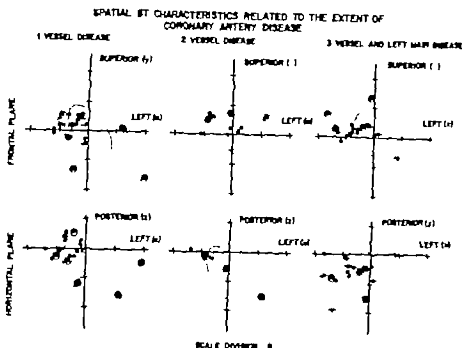


Fig 8 Spatial ST characteristics related to the extent of coronary disease Circles indicate remote myocardial infarction and crossbars (right panel) patients with left main disease

sence of one or more discrete areas of subendocardial and/or transmural ischemia.

III *Relation between the extent of coronary artery disease and combined electrocardiographic and physiological exercise test findings*

It has been suggested by several authors that ST depression exceeding 2 mm (0.2 mV), identifies left main disease with a relatively high accuracy Analysis of published data (22, 24—26) in terms of sensitivity specificity and predictive value (Fig. 8) indicates a moderately effective diagnostic performance. However the use of silent but definite ST abnormality of the ischemic type as an exercise test endpoint—which is consi prudent in many laboratories, including own—obviously invalidates the u Furthermore the severity of the angina cepted as an end point is likely to vary. the variable lead strength of no monitor leads or lead systems another uncontrolled element. Alternate eria are therefore desirable.

We examined the discriminatory pow the complete exercise test data. The sign ance of the ECG response combined w measurements relating to physical work pacity heart rate, blood pressure and lim ing symptoms and signs was tested in a of 108 patients Each patient had a history chest pain and complete angiographic a exercise studies. Thirty six patients were fr from significant coronary artery disease. B sic clinical characteristics are listed in Tab IV There were no significant differences

Table IV
Clinical correlation Series-Basic Patient Characteristics
Extent of Coronary Artery Disease

	None	1 Vessel	2 Vessels	3 Vessels	Left Main	Total
Men	13	10	6	14	8	51
Women	23	9	7	12	6	57
Total	36	19	13	26	14	108

Mean Age 49 years
Documented Myocardial Infarction 1/36 patients without and 35/72 with coronary artery disease.
Current Propranolol Theraphy 16/36 patients without and 31/72 with coronary disease

In summary we have demonstrated a li ted ability of the exercise ECG to localize ocardial ischemia to specific arterial dis bution areas. The relatively tenous anato cal relationship between the site of any teral lesion and the localization of discrete eas of myocardial ischemia, combined with e 180° change in the direction of the ST splacement when subendocardial ischemia comes transmural, most likely accounts for dely scattered ST distributions in one and o vessel disease. Patients with left main or ree vessel disease showed a remarkably iform ST distribution consistent with glo l left ventricular subendocardial ischemia. The demonstration of ischemia at a low rk load level appears to be a useful clinical gn of left main and three vessel disease. We ere unable to identify proximal LAD le ons from the exercise test data.

The combined results emphasize the role of ercise testing as an independent method as a means of quantifying the physiologi l impact of coronary disease rather than as alternative to angiography as a means of rving precise anatomical data. Recent stu es (30, 31) strongly suggest that the exercise st results have considerable prognostic sig ficance which may be at least partially un lated to the anatomical extent of the arterial sease.

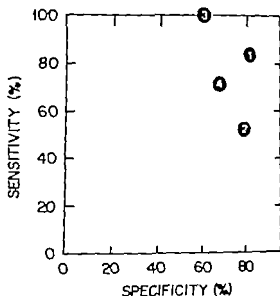
Table VII
Myocardial Ischemia at Low Work Load

Diagnostic Power	Left Main and 3 V vs. 0–2 V	Left Main vs. All Others
Specificity	0.94	0.80
Sensitivity	0.58	0.79
Predictive Value Neg. Test	0.79	0.96
Predictive Value Pos. Test	0.85	0.41

criminatory power as demonstrated in Tables VI and VIII All 36 patients without significant arteriographic disease had a negative result. The predictive values indicate that in the population under study 8/10 patients with a negative test were free from three vessel or left main disease while 8/10 patients with a positive test had three vessel or left main disease. The specificity of the test when used to differentiate patients with left main disease from all others was lower but the predictive value of a negative test was high 0.96 Thus failure of the exercise test to produce ischemia at a low work load level provides strong evidence against left main disease.

Corresponding results were obtained by Nixon et al (28) in a different population (n = 75) studied at the Dallas VA Hospital They used the identical criteria to separate male patients with left main disease from patients with two and three vessel disease. Sensitivity and specificity were 0.64 and 0.80 and the predictive value of a positive test 0.25 and of a negative test 0.96 at an overall prevalence of left main disease of 9 %.

A total of 29 patients in our series had a proximal LAD diameter reduction of ≥ 90 %. A majority or 19 patients had three vessel or left main disease. The presence of severe proximal LAD lesions was associated with a slightly lower functional capacity than in patients with no or lesser degrees of LAD disease and comparable RCA and circumflex lesions However the functional impairment was not of sufficient degree to satisfy the criteria that identified patients with left main and three vessel disease.



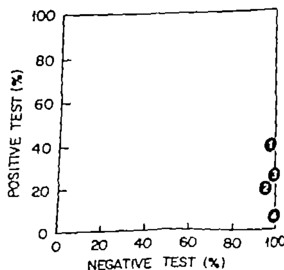


Fig 9 Diagnostic power of ST depression 2 mm in left main coronary disease

tenography and cardiac dynamics. Circ. 46 956, 1972.
BARTEL, A.G BEHAR, V.S., PETER, R.H., ORGAIN E.S., KONG Y Graded exercise stress tests in angiographically documented coronary artery disease. Circ. 49 348 1974
GOLDSCHLAGER, N., SELZER, A., COHN K. Treadmill stress tests as indicators of presence and seventy of coronary artery disease. Ann. Ind. Med. 85 277 1976.
KELEMAN M.H GILLILAN R.E., BROUCHARD R.J HEPPHER, R.L., WARBASSE, J R. Diagnosis of obstructive coronary disease by maximal exercise and atrial pacing. Circ. 48 1227 1973
CHEITLIN M.D DAVIA, J E., de CASTRO C.M., BARROW E.A., ANDERSON W T Correlation of critical left coronary artery lesions with positive submaximal exercise tests in patients with chest pain. Am Heart J 89 305 1975
COHEN M V., GORLIN R. Main left coronary artery disease. Circ. 52 275 1975
DEMOTS H., BONCHER, L.I., RÖSCH, J., ANDERSON R.P., STARR, A., RAHIMTOOLA, S.H. Left main coronary disease Risks of angiography importance of coexisting disease and effects of revascularization. Am J. Cardiol. 36 136 1975
ARESKOG N.H., BJÖRK, L., BJÖRK, V.O HALLEN A., STRÖM, O Physical work capacity ECG reaction to work test and coronary angiograms in coronary artery disease. Acta Med. Scand. 181 Suppl. 472 9 1967
NIXON J V BLOMQVIST C G., LIPSCOMB, K., SHAPIRO W Stress testing in patients with left main coronary disease To be published.
ELLESTAD M H WAN M K.C Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. Circ. 51 363 1975.
MARGOLIS J R. Treadmill stage as a predictor of medical and surgical survival in coronary disease. Circ. 51—52, Suppl. II 109 1975 (Abstract)

REFERENCES

1 SOBEL, B E RESHEMAN G F SHELL, W E., YODER R.D Estimation of infarct size and its relation to prognosis. Circ. 48 588 1973

2. KALBFLEISCH H HORT W Quantitative study on the size of coronary artery supplying areas postmortem Am Heart J 94 183 1977

3 BRUSCHKE, A.V G., PROUDFIT W L. SONES F M Progress study of 590 consecutive non surgical cases of coronary disease followed 5—9 years. Arteriographic correlations. Circ. 47 1147 1973

4 BLOMQVIST G Exercise testing in rheumatic heart disease. Cardiovascular Clinics 5 267 1973

5 STRANDELL, T Heart rate and work load at maximal working intensity in old men *Acta Med Scand. 176 301 1964*

6 SANNE, H Exercise tolerance and *physical training of non-selected patients* after myocardial infarction Acta Med Scand Suppl 551 1973

7 AHA Committee on Exercise (Chairman Kattus A) Exercise testing and training of apparently healthy individuals A handbook for physicians. American Heart Association New York, 1972.

8 *BLOMQVIST G The Frank lead exercise* electrocardiogram A quantitative study based on averaging technique and digital computer analysis Acta Med Scand *Vol 178* Suppl 440 *1965*

9 BLOMQVIST C G., BERGMAN S A. HEMMING C AND TREIBWASSER, *J H ST* and *T wave abnormalities at rest* and during exercise in patients with arteriosclerotic heart disease p 204 in Roskamm H and Reindell H (Eds.) Das chronisch kranke Herz. Schattauer Stuttgart—New York 1973

10 BLOMQVIST C.G., DUNN R A., PIPBERGER, H V SCHWADE, J L. and MURRAY R.G Heart rate, sex and QRS magnitude as *determinants of normal* ST amplitudes during exercise. Circ. *54 Suppl* II 36 1976. (Abstract)

11 BLACKBURN H W The exercise electrocardiogram Technological procedural and conceptual developments p. 220 in Blackburn H W (Ed.) Meas *exercise electrocardiography The* Simonson Conference. Charles C. Thomas Publisher Springfield, 1969

12. McHENRY P L., PHILLIPS, J KNOBEL, S B Correlation of computer-quantitated treadmill exercise electrocardiogram with arteriographic location of coronary artery disease. Am J Cardiol 30 747 1972.

13 *KAPLAN M.A., HARRIS C.N.,* AR*NOW W S.,* PARKER, D.P., FI*TAD M H Inability of the submaximal* stress test to predict the location of coronary artery disease. Circ. 47 250, 1973

14 ATTERHÖG J.H EKELUND L KAIJSER, L. Electrocardiographic abnormalities during exercise three weeks to eighteen months after anterior myocardial infarction Brit. Heart J 33 1971

15 *WOHL, A.J LEWIS H R., CAM*W., KARLSSON E. WILLERSON J T *MULLINS C B.,* BLOMQVIST C.G Cardiovascular function early recovery from acute myocardial infarction Circulation In Press.

16 CHAHINE, R.A., RAIZNER A.E., ISHIMORI T The clinical significance of exercise-induced *ST* elevation. Circ. *54 209 1976*

17 FORTUIN N.J., FRIESINGER, G.C *Exercise-induced ST* elevation. Clinical angiographic and electrocardiographic studies in twelve patients. Am J Med 49 459 1970

18 HEGGE, F TUNA, N., BURCHELL H The correlation of *ST segment* elevations and axis shift in graded treadmill *exercise test with coronary* arteriographic findings. Am J Cardiol 29 269 1972 (Abstract)

19 SIMOONS M L. Computer assisted interpretation of exercise electrocardiograms. *Bronder-Offset BV Rotterdam* 1976.

20 *HOLLAND R., BROOKS H Precordial* and *epicardial surface potentials* in *myocardial ischemia A theoretical and* experimental analysis of the TQ and ST segments. Circ. Res. 37 471 1975

21 MARTIN C.M., McCONAHAY D R. *Maximal treadmill exercise electrocardiography Correlations with coronary ar*

8.

EXERCISE TESTING IN THE DIAGNOSIS OF CORONARY LESIONS PROXIMAL TO THE FIRST DIAGONAL BRANCH OF LAD

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Evidence presented here and elsewhere by Griffith and co workers and the original data of Janushkevichius et al presented here by Bloozhas implicate the proximal part of left anterior descending artery (LAD) as the most frequent site of coronary stenosis associated with sudden cardiac death Depolarization changes in electrocardiographic leads I/aVL and V_{2-4} during episodes of acute ischemia strongly suggest the presence of such lesions (1 2) *It is however unknown how sensitive* and specific these ECG alterations are. Do these ECG changes carry equal significance *if provoked by exercise test?*

The objective of this report is to present some preliminary data from a study in progress *aiming to investigate the above* problems.

MATERIAL

The material consists of 15 patients with severe angina pectoris not responding to ... cal therapy Coronary bypass *surgery* considered and they were admitted for ... luation 14 of them were males and one ... male (No 11) with the age ranging betw... 36 and 64 years (mean 54) The patients w... kept under usual drug therapy at the ... examination All of them were receiving ... tablockers and seven had digitalis. ... ditional clinical data are given in Table I.

METHODS

Exercise test was performed on bicycle ... *gometer with step wise increasing work*[1] The duration of each step was one min...

Table I
Summary of history and ECG at rest.

Group No	Case No	Age yrs	History MI No	HT	Dig	Diu	ECG at rest Q-waves	ST-depression ‡ I/aVL	III,aVF	CH_{24}
I Q-wave in I/aVL V_{23}	1	54	1	−	−	−	I/aVL	+	−	+
	2	57	1	−	+	−	V_{23}	+	−	+
	3	54	2	−	+	+	V_{23},aVF	−	+	+
	4	55	1	+	+	+	V_{23}	+	−	+
II ECG at rest normal. Pos. ET	5	45	1	−	−	−	−	−	−	−
	6	36	0	−	−	−	−	−	−	−
	7	60	0	−	−	−	−	−	−	−
	8	60	1	−	−	−	−	−	−	−
	9	51	0	−	+	−	−	−	−	−
III ECG at rest pathol Group I not included	10	64	0	+	+	+	−	−	+	−
	11	57	0	+	−	+	−	+	+	+
	12	54	2	−	+	−	III,aVF	+	+	+
	13	56	1	−	+	+	III,aVF	−	+	+
	14	56	0	−	+	−	LBBB			
IV ECG at rest and ET normal	15	56	0	+	−	−	−	−	−	−

Abbreviations MI = Myocardial Infarction HT = Hypertension Dig = Digitalis therapy Diu = Diuretic therapy CH_{24} = Bipolar Chest Head leads ET = Exercise test.

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The exercise was discontinued at the point
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s calculated from ECG every minute and
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nal (5).

Coronary arteriography and left ventriculography were performed 1–2 days after exercise testing. The arteriograms were coded according to the American Heart Association grading system (6) The *proximal LAD lesions* was thus defined as a significant obstruction (at least 50 %) localized proximally to and including the origin of first major perforator septal branch. As a rule first diagonal artery was within this area if not, this was specially noted.

RESULTS

The main results are listed in Table I and II Three groups of patients could be distinguished. Group I included patients with ECG signs of previous transmural anterior wall infarction Group II patients had normal ECG

ble II

mary of ECG during exercise and coronary angiogram.

oup	Case No.	ECG during exercise Development or increase of ST-depression. § I/aVL	III,aVF	CH_{2-4}	Coronary arteriography §§ Main LCA	Prox LAD	Dist LAD	LCx	RC
	1	+	+	4–5	–	+	+	–	+
	2	–	+	1–2	–	++	–	–	–
	3	–	+	0	–	++	–	+	+
	4	–	+	1–2	–	–	++ [§§§]	–	–
	5	+	(+)	2–3	–	++	–	+	–
	6	+	(+)	2–3	–	++	–	–	++
	7	+	–	2–3	–	++	–	–	–
	8	+	–	2–3	–	+	+	–	++
	9	+	(+)	2–3	–	++	–	++	–
	10	+	+	3–4	–	+	+	+	++
	11	–	+	2–3	–	–	+	+	+
	12	–	+	1–2	–	–	–	+	+
	13	+	–	1–2	–	–	–	–	+
	14				+	–	–	–	+
	15	–	–	0	–	–	–	–	–

reviations and definitions *Main LCA* = Main Left Coronary Artery
x. *LAD* = Proximal segment of Left Anterior Descending Artery including origin of first major
forator septal branch and, if not commented first diagonal artery
t *LAD* = Segment of LAD distal to origi of first major perforator septal branch.
= Left Circumflex artery
= Right coronary artery
As in Table I. For CH_2 during exercise, ST-depression in mm
++ 99–100% stenosis of main stem
+ ≥ 50% of main stem or major branch
< 50% stenosis or normal artery
First diagonal artery origin from main left coronary artery

Evidence presented here and elsewhere by *Griffith* and co workers and the original data of Janushkevichius et al *presented here by* Bloozhas implicate the proximal part of left anterior descending artery (LAD) as the most frequent site of coronary stenosis associated with *sudden cardiac death* Depolarization changes in electrocardiographic leads I/aVL and V_{2-4} during episodes of acute ischemia strongly suggest the presence of such lesions (1 2) *It is, however unknown* how sensitive and specific these ECG alterations are. Do these ECG changes carry equal significance if provoked by exercise test?

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	2	57	1	–	+	–	V_{2-3}	+	–	+
	3	54	2	–	+	+	V_{2-3}, aVF	–	+	+
	4	55	1	+	+	+	V_{2-3}	+	–	+
II ECG at rest normal, Pos. ET	5	45	1	–	–	–	–	–	–	–
	6	36	0	–	–	–	–	–	–	–
	7	60	0	–	–	–	–	–	–	–
	8	60	1	–	–	–	–	–	–	–
	9	51	0	–	+	–	–	–	–	–
III ECG at rest pathol Group I not included	10	64	0	+	+	+	–	–	+	–
	11	57	0	+	–	+	–	+	+	+
	12	54	2	–	+	–	III aVF	+	+	+
	13	56	1	–	+	+	III aVF	–	+	+
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Abbreviations MI = Myocardial infarction HT = Hypertension Dig = Digitalis therapy Diu = Diuretic therapy CH_{24} = Bipolar Chest Head leads ET = Exercise test.

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	8	+	—	2—3	—	+	+	—	+ +
	9	+	(+)	2—3	—	+ +	—	+ +	—
	10	+	+	3—4	—	+	+	+	+ +
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Lack of ischaemic ST-depression during ex
ise in leads I/aVL and CH_{2-4} correctly
dicted that there was no proximal LAD
ion in four out of six patients. In two pa
nts the exercise test was falsely negative.
ese two patients had abnormal resting
ctrocardiograms and were on digitalis
ne or diuretics and digitalis respectively. It
well known that cardio-active drugs and
normal resting ECG negatively influence
validity of exercise ECG to predict arte-
graphically demonstrable coronary le-
ns.

at rest but developed ST depression in leads I/aVL and CH_{2-4} on exercise. Group III consisted of patients with various ECG abnormalities excluding those with the anterior wall Q waves classified separately into group I Finally there was only one patient with normal ECG at rest and on exercise.

All patients except one (No 13) developed severe chest pain during exercise test. The one who was free of pain during exercise developed it after exercise a usual type of response in this patient.

Maximal heart rate varied between 94 and 146 (mean 108) only one patient reaching 146 while the maximal heart rate in the remaining patients did not exceed 115 There were no marked differences in maximal heart rate between the groups or between patients with different degree of vessel involvement.

There was no difference in maximal systolic blood pressure response or maximal work load. The maximal systolic blood pressure ranged between 150 and 210 mm Hg and maximal work load between 60 and 160 watts

The patient with a main stem lesion (No 14) did not increase heart rate during the last five steps of exercise a sign not seen in other cases. His systolic blood pressure increased however in the usual fashion.

In group I there was one patient (No 1) with a pathological Q-wave in leads I/aVL but not in the precordial leads. There were also three patients with Q-waves in the precordial leads but not in I/aVL. The ST-depression during exercise varied in this group It was most marked in patient No 1 with Q in I/aVL.

The patients of Group II who had normal ECG at rest responded to exercise with 1/2 mm or more ischemic ST-depression in lead I and much more marked ST-depression in the precordial leads. These ST-changes were present immediately (15—20 sec.) after exercise in all patients. No changes could be recorded in the majority of the patients four minutes later

The patients belonging to group III showed one or other types of ECG abnormalities at rest and all of them except for case No 14 had digitalis or/and diuretic treatment in addition to beta blockers. There was only one patient with proximal LAD stenosis (No 10) in this group and he showed progress of ST-depression in lead I/aVL and CH_{2-4} ing exercise. Similar ECG response to ise although less pronounced, was also in case No 13 who had a sign stenosis of right coronary artery and 50 per cent obstruction in the proximal l

In case No 11 with a pronounced ST pression in precordial leads but no leads I/aVL the arteriogram disclosed a stenosis beginning in proximal LAD with than 50 per cent obstruction and progress to more than 50 per cent obstruction in distal part of LAD possibly including the first diagonal artery Patient No. 12 w two old posterior infarctions showed ST-depression in leads I/aVL and had significant disease of proximal LAD Pa No 14 had left bundle branch block, mak further interpretation of ST-changes imp ible abnormal heart rate response to was of diagnostic value

Patient No 15 had a normal ECG a and on exercise. The coronary was also normal

DISCUSSION AND CONCLUSIONS

First of all it should be emphasized that computer program for noise reduction, bilization of base line and ECG averag was highly effective permitting a convenie interpretation and reading of all leads and during exercise. ST segment deviat from the reference level by 0 5 mm or was easily recognized and measured

Occurrence or progression of already exist ing ST-depression during exercise in lead I/aVL and CH_{2-4} were predictive of signifi cant (50 per cent) proximal LAD stenosis in seven out of eight patients. Only one fals positive case appeared to be present, but ac tually this patient (No. 13) also had a proxi mal LAD stenosis which was judged to be insignificant (< 50 per cent).

9.

NON INVASIVE DETECTION AND EVALUATION OF THE FUNCTIONAL SEVERITY OF CORONARY ARTERY DISEASE THE ROLE OF RADIONUCLIDE CINEANGIOGRAPHY DURING EXERCISE

Jeffrey S. Borer M.D.,
Stephen L. Bacharach, Ph D.,
Michael V Green, M.S.,
Kenneth M. Kent, M D., Ph.D.,
Bonnie Mack, M.S., and
Stephen E. Epstein, M.D
With the technical assistance of
Susan Farkas, B.S

From the National Institutes of Health, NHLBI Cardiology Branch Bethesda, Md

REFERENCES

1 ANGELL, C.S., GRIFFITH L.S.C. teroseptal myocardial ischemia as a c of ventricular fibrillation or tachycar Circulation 53 54 Suppl. II 674 197

2. GRIFFITH, L.S C., PLATIA, E.V GELL, C.S GRUNWALD L.B.A. (ronary arteriographic and ographic correlates of sudden death For publication presented at meeting of the European Coronary gery Study Group Sweden, Sept. 1977

3 BINKHORST R.A., and VAN LEE WEN P A rapid method for the de mination of aerobic capacity ale Zeitschrift für angewandte Physio einschliesslich Arbeits-physiologie, 459 1963

4 ASTRÖM H., JONSSON B. Design exercise test, with special reference heart patients. Brit. Heart J 38(3), 1976

5 JANSSON L. JOHANSSON K., JO SON B OLSSON L.G., WERNER, and WESTLING H Computer ass ance in the ECG laboratory—a new Scand J Clin. Lab Invest 36 Suppl. 1976

6 AHA committee report. A reporting tem on patients evaluated for tery disease. Circulation 51 2, 1975.





re 2 Unretouched selected frames, in sequence a radionuclide cineangiogram taken in a pa- with three-vessel coronary-artery disease at (upper) and during maximal exercise (lower) (Abbreviations as in Figure 1). (Figure and legend reprinted by permission from the New England Journal of Medicine 296 841 1977).

es of images (framing rate up to 100 mes/sec). These images, which reside in core memory of the computer span the rage cardiac cycle. While data are being uired, the images can be displayed as an dless-loop, flicker free movie (Figure 1 2). is allows immediate access to qualitative ormation regarding spatial and temporal rations of the cardiac chambers. Visually erpretable information is produced within seconds of the onset of data collection d statistically reliable results within one to o minutes.[3] Thus, data collection is suffi ntly rapid to permit the procedure to be plied to studies during exercise induced is emia and angina which might preclude olonged exercise and imaging.

While the cardiac images are being created computer simultaneously analyzes the ac red data to produce a time-activity curve th high (10 msec) temporal resolution [2] gure 3). Corrections for background activ are made as previously described.[5] Since od radioactivity is proportional to blood lume after correction for background the e-activity curve in fact represents a mea e of left ventricular volume versus time. erefore, once the physician has identified left ventricle in the end-diastolic movie me, quantitation of left ventricular volume nge with time can be performed. In order obtain statistically reliable information, the computer sums the radioactivity in the ventricle during many beats. After each car diac cycle the length of the RR interval is automatically examined to determine if it lies

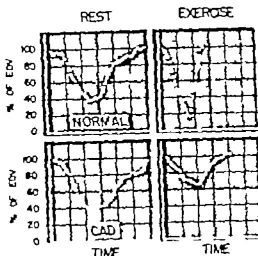


Figure 3 Effect of exercise on left ventricular func tion left ventricular time-activity curves from stu dies shown in Figures 1 and 2 EDV denotes end-diastolic volume Note that ejection fraction

$$\frac{(\text{EDV}-\text{end-systolic volume})}{\text{EDV}}$$

increases with exercise in th normal subject and decreases with exercise in the patient with coronary artery disease (CAD) (Figure and legend reprinted by permission from the New England Journal of Medicine 296 842 1977).

While the presence of coronary arterial narrowing which indicates regions of potential myocardial ischemia can be detectd by coronary arteriography determination of the presence and severity of ischemia requires assessment of left ventricular function

However such assessments most commonly have been invasive, and have been associated with practical limitations which preclude routine or repeated evaluation and which most often have necessitated that studies be performed with the patient at rest. Since, even in the presence of relatively severe stable coronary artery disease left ventricular function is normal or near normal with the patient at rest an accurate indication of the presence and functional importance of ischemic heart disease requires study during stress such as that imposed on the heart by exercise.

Recently we have developed a real time radionuclide imaging system [1-3] which permits analysis of regional and global left ventricular function during intense exercise [4] The technique involves acquisition with immediate display and analysis, of multi image electrocardiographically gated scintigrams in endless loop flicker free movie format This imaging system has now been utilized in the study of more than 600 patients[4-8] with various forms of heart disease, and has pr particularly valuable in the detection of tionally important lesions ... teries.[4-6]

RADIONUCLIDE CINEANGIOGRA METHODOLOGY

Gated cardiac scintigraphy is perf subjects in the supine position at during exercise. This procedure is mad intravenous administration of albumin labelled with 10 mCi of radioac technetium (Tc[99m]). After a period of 5 tes to permit equilibration of the tracer blood pool a conventional Anger (field of view = 254 mm diameter) with a high sensitivity parallel hole colli tor is oriented in the modified left oblique position [1-3] which permits of the left ventricle in the field of view aging then is accomplished at rest and exercise by the use of our compu electrocardiographically gated dure [1-3] modified to reduce data pro time and the interval required to achiev istical reliability [3,4] The spatial resolu this system is one centimeter

When this procedure is employed, data a collected and concurrently organized

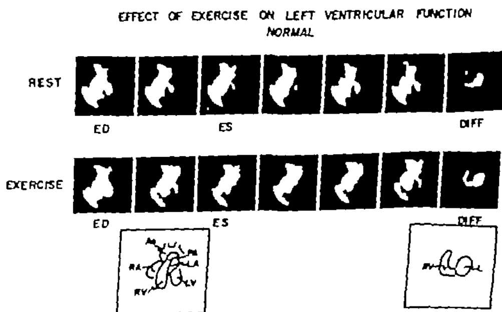


Figure 1 Unretouched selected frames in sequence from a radionuclide cineangiogram taken in a normal subject at rest (upper) and during maximal exercise (lower) ED denotes end-diastolic frame ES end-systolic frame DIFF difference image (created by electronic subtraction of end systolic counts from end-diastolic counts) AO aorta PA pulmonary artery RA right atrium RV right ventricle LA left atrium and LV left ventricle (Figure and legend reprinted by permission from the New England Journal of Medicine 296 841 1977

OF STUDIES IN PATIENTS CORONARY ARTERY DISEASE

earliest studies demonstrated that, when ied during exercise the technique can be to determine the presence and location angiographically demonstrable (50 % oses of the coronary arteries even in pa s whose regional and global left ventri r function are normal at rest[4] (Table 1). In ition, these early studies demonstrated in patients with coronary artery disease response is directionally opposite to that normal subjects, and that the ejection frac developed during exercise in such pa ts is almost invariably below the range ieved by normal subjects (Figure 4)

These results have been confirmed and ex ded in subsequent studies of larger groups ients and normal subjects.[5,6] These later dies have demonstrated that the technique mits assessment of the degree of dysfunc n in a given region, thus aiding in the elu lation of areas of potentially critically se ischemia.[3] Such abnormalities of regio l function are themselves diagnostic of ischemic heart disease since they are seen only in association with lesions in vessels supply ing the abnormally functioning regions and are not seen in normal subjects or in regions supplied by normal arteries in patients with other stenotic vessels. Moreover regional abnormalities have been found during exercise even at levels of exertion not associated with symptoms.[3] Thus, in one study all 47 patients with coronary artery disease manifested regional dysfunction during exercise though 14 did not develop angina pectoris during the exercise study Moreover ejection fraction in these 47 patients decreased from 48 % at rest to 36 % during exercise ($p < .001$) while in 25 age-matched normal subjects, ejection fraction invariably increased with exercise (av 57 % at rest, 71 % during exercise, $p < .001$), and no regional dysfunction was noted.[3] It is not surprising, therefore, that we have found radionuclide cineangiography during exercise to be more sensitive and more predictive than exercise electrocardiography in the diagnosis of coronary artery disease.[6]

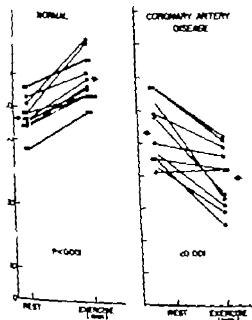


Figure 4 *Effect of exercise on left ventricular systolic ion showing the change in ejection fraction to maximal exercise in normal subjects and patients with coronary-artery disease (represents mean ejection fraction for entire group). (Figure and legend reprinted, by permission, from the England Journal of Medicine 296 842, 1977).*

Our studies also have demonstrated the utility of the technique in assessing the effect of therapeutic intervention.[5,10] Thus, the sublingual administration of nitroglycerin has been shown to improve regional and global left ventricular function not only at rest but also and quantitatively more impressively during intense exercise, when ischemia would be most likely to be present.[5] Thus, in 28 patients given nitroglycerin ejection fraction during exercise before drug administration averaged 36 % average ejection fraction rose to 48 % during exercise after nitroglycerin. It is of interest that ejection fraction during exercise in normal subjects was unaffected by nitroglycerin. Moreover the beneficial effects of nitroglycerin were manifest even in patients who did not develop chest pain with exertion.[5] Similarly in many patients radionuclide cineangiography after coronary artery bypass grafting has demonstrated alleviation of regional and global dysfunction encountered during exercise prior to operation though no change has been noted in left ventricular function at rest in comparing pre and post-operative assessments.[10]

CLINICAL IMPLICATIONS

Stenoses of the coronary arteries can produce clinically important imbalance between myo-

within a physician selected temporal beat length "window" Distortion of the time activity curve by premature beats is prevented by rejection of cycles falling outside this window The movie can be similarly windowed. Ejection fractions obtained by this method show excellent correlation with those obtained by contrast angiography with the patient at rest ($r = 0.92$, $p < .01$).[9]

After the images and time activity curves are obtained at rest, the subjects begin to pedal a bicycle ergometer In the studies to be described imaging was continued for at least two minutes, until development of fatigue or typical angina of severity customarily causing the patient to stop exercising.

After completion of imaging, left ventricular ejection fractions at rest and during exercise automatically are determined from the computer-generated time-activity curves regional left ventricular function, at rest and during exercise, is determined visually from movies.

Since movies most often are constructed from images obtained in the modified left anterior oblique position function of only the anteroseptal and anterolateral walls can be evaluated from the movie. sessment of other surfaces of the heart car achieved by creating movies from images tained with the camera oriented in ... other than modified left anterior obliq however to assess those regions which do lie on the edges of the cardiac silhouette in left anterior oblique position, our stand approach involves analysis of count-based "difference images" created by the end-systolic image from the end- image[2] (Figure 1 2). In the resulting ence image the intensity (brightness) of region of the image is proportional to absolute change in radioactive emi (volume) between diastole and systole in region. In the left anterior oblique view non-edge-bordered defect (that is, a region darkness located centrally in the image and surrounded by bright regions) cessarily indicates the presence of either posterobasal or anterobasal region f which blood is not being ejected (i e., is not being ejected in as great a qu as from surrounding regions)

Table 1

Correlation between Coronary Arteriographic and Exercise Radionuclide Cineangiographic Abnormalities.*

Case No.	Age (Yr)	FC Nyha †	Coronary Arteriographic Analysis ‡			Exercise Radionuclide Cineangiogram Analysis		Exercise Difference Image Analysis (Non Edge Bordered Defect)
			LAD	LCC	RCA	Antero-special dysfunction	Antero-lateral dysfunction	
1	49	II	+	+		+	+	+
2	37	II	+			+		
3	62	III	+§	+§	+	+	+	+
4	51	III	+	+	+	+	+	+
5	50	II	+	+	+	+	+	+
6	56	II	+	+	+	+	+	
7	52	III	+	+	+	+	+	+
8	40	II	+		+	+		
9	68	IV	+	+	+	+	+	
10	40	II	+			+		
11	50	I	+		+	+		+

+ denotes abnormality present & no entry abnormality absent. † New York Heart Association Functional Class. ‡ Arteries with >50% occlusions. LAD denotes left anterior descending coronary artery, LCC left circumflex coronary artery & RCA right coronary artery §Left main coronary artery >50% occlusion, in addition to LAD & LCC.

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SULTS OF STUDIES IN PATIENTS TH CORONARY ARTERY DISEASE

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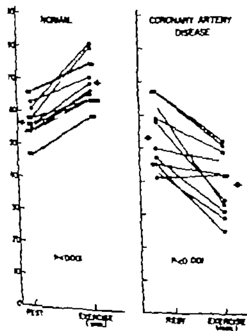


Figure 4. Effect of exercise on left ventricular systolic action showing the change in ejection fraction on rest to maximal exercise in normal subjects and patients with coronary-artery disease (◆ repre- nts mean ejection fraction for entire group). (Fi- re and legend reprinted by permission, from the New England Journal of Medicine 296: 842, 1977).

chemic heart disease since they are seen only in association with lesions in vessels supplying the abnormally functioning regions and are not seen in normal subjects or in regions supplied by normal arteries in patients with other stenotic vessels. Moreover, regional abnormalities have been found during exercise even at levels of exertion not associated with symptoms.[5] Thus, in one study all 47 patients with coronary artery disease manifested regional dysfunction during exercise, though *14 did not develop* angina pectoris during the exercise study. Moreover, ejection fraction in these 47 patients decreased from 48 % at rest to 36 % during exercise ($p < .001$), while in 25 age matched normal subjects, ejection fraction invariably increased with exercise (av 57 % at rest, 71 % during exercise, $p < .001$) and no regional dysfunction was noted.[5] It is not surprising, therefore, that we have found radionuclide cineangiography during exercise to be more sensitive and more predictive than exercise electrocardiography in the diagnosis of *coronary artery disease*.[6]

Our studies also have demonstrated the utility of the technique in assessing the effect of therapeutic intervention.[5,19] Thus, the sublingual administration of nitroglycerin has been shown to improve regional and global left ventricular function not only at rest but also, *and quantitatively more impressively*, during intense exercise, when ischemia would be most likely to be present.[5] Thus, in 28 patients given nitroglycerin, ejection fraction during exercise before drug administration averaged 36 %; average ejection fraction rose to 48 % during exercise after nitroglycerin. It is of interest that ejection fraction during exercise in normal subjects was unaffected by nitroglycerin. Moreover, the beneficial effects of nitroglycerin were manifest *even in patients who did not develop* chest pain with exertion.[5] Similarly, in many patients radionuclide cineangiography after coronary artery bypass grafting has demonstrated alleviation of regional and global dysfunction encountered during exercise prior to *operation* though no change has been noted in left ventricular function at rest in comparing pre and post-operative assessments.[19]

CLINICAL IMPLICATIONS

Stenoses of the coronary arteries can produce clinically important imbalance between myo-

cardial oxygen supply and demand. However such abnormalities most commonly are present only during stress when stenotic vessels are incapable of permitting augmentation of flow to maintain myocardial oxygen supply at a level sufficient to meet increased demand Radionuclide cineangiography performed during the physiologic stress of exercise permits determination of the reserve capacity of the coronary circulation to meet such increasing demands and thus provides an accurate non invasive means of evaluating the functional importance of coronary artery lesions The technique is effective in the detection of coronary artery disease and in the evaluation of the efficacy of therapy and would be expected to prove of value in the determination of prognosis.

It should be emphasized that while abnormalities of regional function are seen only in areas supplied by coronary arteries with 50 % stenoses, it is not true that all regions supplied by diseased arteries function abnormally nor that similar degrees of dysfunction are seen in all regions supplied by arteries with angiographically similar degrees of stenosis. Such variation in regional function might be attributable to variations in collateral supply or to variation in the actual degree of cross-sectional narrowing of vessels with angiographically similar stenoses.[4] Because it provides a functional assessment of the importance of any coronary artery lesion and because it permits the physician to distinguish the relative functional importance of anatomically similar coronary artery lesions radionuclide cineangiographic assessment might prove a particularly useful method in the identification of those lesions which are potentially critical and which might be most likely to be associated with sudden death

REFERENCES

GREEN M.V., OSTROW H.G., DOUGLAS, M.A., et al High temporal resolution ECG-gated scintigraphic angiocardiography J Nuclear Med. 16 95–98, 1975.

GREEN M V BACHARACH S.L., DOUGLAS M.A., et al The measurement of left ventricular function and the detection of wall motion abnormalities with high temporal resolution ECG-gated scintigraphic angiocardiography IEEE Transac Nuclear Sci 23 1257–1263, 1976.

BACHARACH S.L., GREEN M V., BORER, J.S., et al A real time system for multi-image gated cardiac studies. J Nuclear Med. 18 79–84 1977

BORER, J.S., BACHARACH S L., GREEN M V., et al Real time radionuclide cineangiography in the non invasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl. J Med. 296 839–844 1977

BORER, J.S., BACHARACH S.L., GREEN M.V et al Effect of nitroglycerin on exercise-induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease assessment by radionuclide cineangiography in symptomatic and asymptomatic patients. Circulation, in press (February 1978).

BORER, J.S., KENT K.M BACHARACH S.L., et al Accuracy of radionuclide cineangiography in detecting coronary artery disease comparison with exercise electrocardiography Circulation 56 Suppl. III III–33 1977 (Abs.).

BORER, J.S., BACHARACH S L., GREEN M V et al Exercise-induced left ventricular dysfunction in symptomatic and asymptomatic patients with severe aortic regurgitation assessed by radionuclide cineangiography Am. J Cardiol. 39 284 1977

8 BORER, J.S., BACHARACH S.L., GREEN M.V et al Evaluation of clinical utility of real-time computer based radionuclide cineangiography Computers in Cardiology Rotterdam, 1977 in press.

9 GREEN M.V., BACHARACH, S.L., BORER, J.S., et al A count-based method for determination of ejection fraction from radionuclide scintigrams. J Nuclear Med in press.

10 KENT K.M., BORER, J.S., GREEN M V., et al Effects of coronary artery bypass operation on global and regional left ventricular function during exercise Clin. Res. 25 230A, 1977

10.

THALLIUM[201] EXERCISE TESTING IN CORONARY ARTERY DISEASE

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ABSTRACT

Myocardial imaging was performed following intravenous administration of Thallium[201] (Tl[201]) at rest and during maximal exercise testing in 39 patients presenting with chest pain. Image data were computer analysed and compared with the results of coronary arteriography and left ventriculography

In 26 patients with coronary artery disease (CAD) Tl[201] perfusion defects were present in 12 at rest and 24 on exercise In 13 patients with normal vessels, perfusion defects were present in 2 at rest and one on exercise.

Resting Tl[201] image data corresponded to the presence or absence of impaired LV wall motion in 21 of 26 patients with coronary artery disease. Exercise scans were more accurate than rest scans in detecting the presence of CAD (Tl[201] scintigram—rest sensitivity—46 % exercise sensitivity—92 %, $P < 0.005$) Perfusion defects on the exercise Tl[201] scintigram tended to reflect the distribution of vessel disease, but prediction of individual coronary lesions from the scan findings was not possible.

These data suggest that Tl[201] myocardial imaging is a useful non-invasive technique for the investigation of patients presenting with chest pain Rest Tl[201] scintigrams correspond to LV appearance on the ventriculogram and perfusion defects on the exercise Tl[201] scintigram detect the presence of CAD

Radionuclide myocardial imaging provides a non invasive technique for the investigation of patients with suspected coronary artery disease. Regional myocardial perfusion can be evaluated by imaging with a variety of agents (K^{43} Rb^{81} Cs^{129}) (2, 3 5 10 16 19 20 26) Thallium[201] (Tl[201]) has physical and biological advantages over other currently available tracers (4 13) and Tl[201] scanning is proving useful in the detection of myocardial infarction (9 17 23 24 26) & stress induced ischaemia (1 11 15 21)

This study was designed to assess Tl[201] perfusion scintigraphy in predicting the presence or absence of coronary artery disease in patients presenting with chest pain. Scintiscans were obtained at rest and following exercise testing. Selective coronary arteriography and left ventriculography were performed in all patients and the results of the radionuclide and angiographic studies pared.

PATIENTS AND METHODS

39 patients presenting with a history of pain sufficiently disabling to merit arteriography were studied 37 patients male 2 female mean age 46 7 years ± (mean ± SEM) range 27–57 years. scintiscans were obtained at rest and following exercise testing with an interval of at 5 days between rest and exercise study rest and exercise studies were within 14 days of cardiac catheterisation. experimental nature of the study was plained to each patient and informed ... obtained.

Radionuclide Studies

Thallium[201] scintiscans were obtained at and following symptom limited maxima... ercise testing.

Exercise Testing

Continuous multistage exercise testing performed using a graded bicycle with initial work load of 300 KPM/min increments of 300 KPM/min at 3 tervals. The electrocardiogram (modified electrode) was monitored continuously ... sampling at 3' intervals and at the end exercise. The tests were discontinued chest pain (94 %) or dyspnoea (6 %)

The exercise electrocardiogram was preted independently without knowledge the results of Tl[201] scan or angiography ... test was considered positive where there horizontal or downsloping ST segment pression more than or equal to 1 m.m. d... or after exercise.

Myocardial Imaging

Scintiscans were performed following the ... travenous injection of 2 mCi Thallium[201] ... lowing a four hour fast, the rest injection ... given in the upright position to minimise ... patic and gastric activity The exercise inj... tion was given at the onset of symptoms an... the exercise terminated 30 seconds thereaft...

Myocardial imaging was performed usin... an Ohio Nuclear Series 100 Gamma Camer... with a high resolution medium sensitivity ...

llel hole collimator Scans were obtained in e anterior 30° and 60° left anterior oblique d left lateral projections. The Gamma was interfaced to a Varian 620L com er and the data were stored on magnetic for later retrieval. Using the computer interest were drawn corresponding anatomical areas of the left ventricle in the four scintigraphic projections ich have been previously described by ers and De Jong (25). The nuclide up in each of these areas was measured and computer analysis expressed as counts per area. In each view the area of maximal clide uptake was accepted as 100 % and the in the remaining anatomical areas ex d as a percentage of this. In order to ne the criteria of normal perfusions 15 bly normal subjects were studied at and 10 after exercise testing.

In both rest and exercise scans, the uptake area to area varied by less than 15 %. attention was paid to the apical ne where visibly reduced uptake has been iously noted as a variant of normal (6). en in this area, the count per unit area was less than 85 % of that in the area of maxi al uptake. Thus, a perfusion defect was con present in any area where this count unit area was less than or equal to 80 % of e activity in the area of maximal nuclide

Perfusion defects seen in the anterior an and septal areas were interpreted indicating disease of the left anterior de ending coronary artery in the inferior area right coronary artery disease in the poste and posterolateral areas as left circum disease.

ardiac Catheterisation

ane left ventriculography and selective arteriography were performed by percutaneous femoral technique. Left wall motion was assessed visually the right anterior oblique and left lateral jections at rest in the supine position Ab- ality was defined as any impairment of l motion ranging from hypo — to dyskine

Significant coronary artery disease was dered present in any vessel where lumi- diameter was reduced by 50 % or more. or the purposes of this study the right coronary artery (RCA) main left coronary artery (main (L)), left anterior descending (LAD) and left circumflex (LCx) coronary arteries were analysed. Patients with coronary artery disease were classified as having single, double or triple vessel disease according to the results of arteriography

RESULTS

Radionuclide Studies

Satisfactory Tl²⁰¹ scintiscans were obtained in all patients at rest and after exercise testing. Perfusion defects were present in the resting Tl²⁰¹ scan in 14 patients and in the exercise Tl²⁰¹ scan in 25 patients. In 20 patients, the distribution of the perfusion defects was more extensive on the exercise study than on the rest study

Typical image data are represented in Fig. 1 Panels a and c illustrate scans taken in this anterior projection after exercise and at rest respectively Panels b and d illustrate scans from the same patient taken in the 30° LAO projection after exercise and at rest respec tively This patient was shown to have a nor mal left ventriculogram and an isolated > 50 % lesion of LAD The rest studies (c and d) show homogeneous myocardial nuclide uptake. However both exercise studies (a

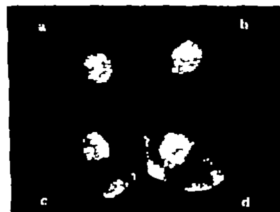


Figure 1 TYPICAL Tl²⁰¹ IMAGE DATA Scans obtained in a patient with normal L.V wall motion and an isolated significant lesion of LAD Panel a and c taken in anterior projection Panel b and d taken in 30° LAO projection Rest study — c and d exercise study a and b Note homogenous nuclid uptake in anatomical areas of L.V in rest study Perfusion defect with reduced nuclide uptake developed in the septal areas in exercise study corresponding to the disease of L.A.D

ABSTRACT

Myocardial imaging was performed following intravenous administration of Thallium[201] (Tl^{201}) *at rest and during maximal exercise* testing in 39 patients presenting with chest pain Image data were computer analysed and compared with the results of coronary arteriography and left ventriculography

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Myocardial imaging was performed using an *Ohio Nuclear Series 100 Gamma Camera* with a high resolution medium sensitivity pa[...]

Table V

COMPARISON OF EXERCISE Tl^{201} SCAN FINDINGS AND CORONARY ARTERY DISEASE IN 26 PATIENTS WITH SIGNIFICANT CAD

Vessel Disease		Exercise Tl^{201} Scan	
		Abnormal	Concordant with Distribution of Vessel Disease
Single	6	6	6
Double	15	14	12
Triple	5	4	—

exercise Tl^{201} scan. However 2 patients with double vessel disease and 4 patients with triple vessel disease had an area of myocardium apparently normally perfused, but supplied by a significantly diseased artery Two other patients (1 double 1 triple vessel disease) with extensive CAD had normal Tl^{201} studies. In addition, although diseased vessels were usually associated with appropriate perfusion defects in the exercise Tl^{201} scan the converse was not reliable i.e. prediction of the individual diseased coronary artery by the location of underperfused areas was not accurate. This was particularly evident in RCA and LCx disease. 4 patients with disease of RCA, but not LCx had perfusion defects both inferiorly and posteriorly Whilst, one patient with LCx, but not RCA disease had identical i.e. inferior and posterior defects.

Although the resting Tl^{201} scan was an insensitive test in suggesting the presence of coronary artery disease, the resting Tl^{201} scan findings tended to correspond to left ventricular wall motion seen in the ventriculogram (Fig. 2). Areas of impaired LV wall motion were present in 13 patients on the resting left ventriculogram (Table II). Perfusion defects were present in the resting Tl^{201} scan in 12 patients. In 10 of these patients, the site of the perfusion defects seen in the scan corresponded to areas of impaired left ventricular wall motion on the ventriculogram 3 patients, all with impaired inferior LV wall motion had normal rest Tl^{201} scans whilst 2 patients with normal LV wall motion had perfusion defects (one anteroseptal + inferior and one antero-apical). 13 patients had normal left ventriculograms, 14 patients had normal rest Tl^{201} scans and in 11 of these patients both the scan

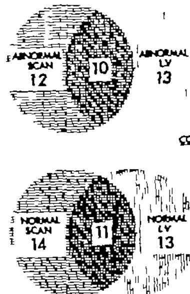


Figure 2 COMPARISON OF REST Tl^{201} SCAN DATA AND L.V WALL MOTION ON LEFT VENTRICULOGRAPHY IN 26 PATIENTS WITH SIGNIFICANT CORONARY ARTERY DISEASE. In 10 patients with perfusion defects on the rest Tl-201 scan the location of the perfusion abnormality corresponded to the site of impaired L.V wall motion on the ventriculogram. In 11 patients note the Tl-201 scan at rest and the left ventriculograms were normal

and LV were normal Overall, therefore the resting Tl^{201} scan findings correspond to the presence or absence of impaired LV wall motion in 21 of 26 patients with coronary artery disease.

DISCUSSION

Increasing emphasis is being placed upon non-invasive techniques to identify patients with significant coronary artery disease. Myocardial imaging following the administration of radionuclide tracers provides a relatively non-invasive means of estimating regional myocardial perfusion (2, 3 5 10 16 19 20 26). Of the currently available tracers, Tl^{201} appears to be one of the most promising (18), and Tl^{201} scintigraphy is proving useful in detecting myocardial infarction (9 17 23 24 26) and stress induced ischaemia (1 11 15 21).

This study demonstrates that image data from Tl^{201} exercise scintigraphy can predict the presence or absence of coronary artery

and b) reveal reduced nuclide uptake in the septal wedge corresponding to the significant disease of LAD

Angiographic Data

26 patients had significant coronary artery disease whilst 13 patients had normal coronary vessels or minor disease. 6 patients had single vessel disease (3 RCA 3 LAD) 15 double vessel disease (7 LAD + RCA 4 LAD + LCx 4 RCA + LCx) and 5 had triple vessel disease (LAD + RCA + LCx) (Table I) Isolated LCx disease was not encountered.

Table I

Category of Vessel Disease		Distribution of Disease
Single	6 patients	3 RCA
		3 LAD
Double	15 patients	7 LAD + RCA
		4 LAD + LCx
		4 RCA + LCx
Triple	5 patients	LAD + LCx + RCA

RCA Right Coronary Artery
LAD- Left Anterior Descending Coronary Artery
LCx Left Circumflex Coronary Artery

In the 26 patients with coronary artery disease, LV wall motion on the resting left ventriculogram was normal in 13 and impaired in 13 patients. In 6 patients the anterior LV surface was involved in 3 patients the inferior surface and 4 patients the abnormality extended anteriorly to inferiorly (Table II)

Table II
LEFT VENTRICULOGRAPHIC FINDINGS IN 26 PATIENTS WITH SIGNIFICANT CAD

Left Ventriculogram			Number of patients
Normal			13
Abnormal	Anterior Surface	6	
	Inferior surface	3	13
	Anterior Inferior Surface	4	

Comparison of Data

In the 26 patients with significant c[illegible] artery disease perfusion defects were pre[illegible] in the resting Tl^{201} scan in 12 patients [illegible] and in the exercise Tl^{201} scan in 24 pat[illegible] (92 %) (Table III) Perfusion defects [illegible]ing the presence of CAD were si[illegible]

Table III
Tl^{201}SCAN FINDINGS IN 26 PATIENTS W[illegible] CORONARY ARTERY DISEASE

	Abnormal Scan	N[illegible] Sca[illegible]
Tl^{201} Scan—Rest	12 (46 %)	14
Tl^{201} Scan—Exercise	24 (92 %)	2

*$p < 0.005$ — Perfusion defects significantly [illegible] frequent in exercise scan compared to rest

more frequent in the exercise scan [illegible] resting scan (24 patients—Exercise scan [illegible] patients—Rest scan $p < 0.005$). 2 [illegible] one with triple vessel disease and one w[illegible] disease of RCA + LAD had normal [illegible] scans both at rest and exercise.

In 13 patients with normal coronaries, [illegible] minor disease the Tl^{201} scan was normal in [illegible] patients at rest and in 12 patients [illegible] ise (Table IV) 2 patients with normal [illegible]nary arteries had perfusion defects anter[illegible] in the resting Tl^{201} scan one of which [illegible] persistently present in the exercise Tl^{201} [illegible] Both patients had abnormal exercise ECG.

6 patients had single, 15 double and 5 [illegible] vessel disease. In 18 of those 26 pati[illegible] fusion defects in the Tl^{201} exercise scan we[illegible] located in anatomical areas which [illegible] ded to vessel disease (Table V). All 6 patien[illegible] with single vessel disease and 12 of the [illegible] patients with double vessel disease had [illegible]propriately sited underperfused areas

Table IV
Tl^{201} SCAN FINDINGS IN 13 PA[illegible] WITH NORMAL CORONARY ARTERIES MINOR CORONARY DISEASE (< 50% OC[illegible]LUSION)

	Normal Scan	Abnormal Scan
Tl^{201} Scan — Rest	11	2
Tl^{201} Scan — Exercise	12	1

REFERENCES

BAILEY I K., GRIFFITH L.S.C., STRAUSS H W PITT B. Detection of coronary artery disease and myocardial ischaemia by electrocardiography and *myocardial perfusion scanning* with Thallium 201 (abst.). AMER. J CAR DIOL 37 118, 1976.

BECKER, L., FERREIRA, R., THOMAS M. Comparison of ^{81}Rb and microsphere estimates of left ventricular blood flow distribution. J NUCL. MED 15 969 1974

BOTVINICK, E.H., SHAMES D M., GERSHENGORN K.M., CARLSSON E., RATSHIN R.A., PARMLEY W W Myocardial stress perfusion scintigraphy with Rubidum – 81 versus stress electrocardiography AMER. J CARDIOL. 39 364, 1977

BRADLEY MORE, P R., LEBOWITZ, E., GREENE, M.W., ATKINS H.L., ANSARI A.N Thallium^{201} for medical use II Biological behaviour J NUCL MED 16 156 1975

CARR, E.A., GLEASON G SHAW J., KRANTZ, B. The direct diagnosis of myocardial infarction by photoscanning after administration of Cesium – 131 AMER. HEART J 68 627 1964

COOK, D.J., BAILEY I., STRAUSS H.W ROULEAU J., WAGNER, H N Jr PITT B Thallium^{201} for myocardial imaging appearance of the normal heart. J NUCL. MED 17 583 1976.

GOULD K., HAMILTON G W., LIPSCOMB, K., RITCHIE, J L., KENNEDY J W Method for assessing stress induced regional malperfusion during coronary arteriography AMER. J CAR DIOL 34 557 1974

GOULD K.L., LIPSCOMB K., HAMILTON G.W Physiologic basis for assessing critical coronary stenosis. AMER. J CARDIOL 33 87 1974

HAMILTON G.W., TROBAUGH G.B., RITCHIE, J L., WILLIAMS D L., WEAVER, W D., GOULD K.L. Myocardial imaging with intravenously injected Thallium 201 in patients with suspected coronary artery disease analysis of technique and correlation with electrocardiographic, coronary anatomic and ventriculographic findings. AMER. J CARDIOL. 39 347 1977

10 HURLEY P.J., COOPER, M., REBA, R.C., POGGENBURG K.J., WAGNER, H N Jr ^{43}KC1 a new radiopharmaceutical for imaging the heart. J NUCL. MED 12 516 1971

11 JAMBROES G., VRIJK, P.P., vd BERG C.J.M., d GRAFF C.N Thallium 201 rest and exercise scintigraphy in patients with coronary heart disease (abst) *CIRC. 52 II – III 1975*

12. KEMP H G., VOKONAS P.S., COHN P F., GORLIN R. The anginal syndrome associated with normal coronary arteriograms. AMER. J MED 54 735 1973

13 LEBOWITZ, E., GREENE, M W., FAIRCHILD R., BRADLEY MORE, P R., ATKINS H.L., ANSARI A.N., RICHARDS P., BELGRAVE, E. Thallium 201 for medical use. I. J NUCL. MED 16 151 1975

14 LIKOFF W., SEGAL, B.L., KASPARIAN H Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. N E.J.M 276 1063 1967

15 McLAUGHLIN P R., MARTIN R.P., DOHERTY P., DASPIT S., GORIS M., HASKELL, W., LEWIS S., KRISS J P HARRISON D C. Reproducibility of Thallium-201 myocardial imaging. CIRC 55 497 1977

16. MARTIN N D ZARET B.L., McGOWAN R.L., WELL, H P FLAMM M D Rubidum^{81} a new myocardial scanning agent. *RADIOLOGY 111 651 1974*

17 PARKEY R.W., BONTE, F.J., STOKELY E.M., LEWIS S.E., GRAHAM K.D., BUJA, L.M. WILLERSON J T Acute myocardial infarction imaged with 99 m Tc – stannous pyrophosphate and ^{201}Tl a clinical evaluation. J NUCL. MED 19 771 1976

18. PITT B., STRAUSS H W Myocardial imaging in the non invasive evaluation of patients with suspected ischaemic heart disease. AMER. J CARDIOL. 37 797 1976.

19 POE, N D Comparative myocardial uptake and clearance characteristics of

disease in patients presenting with chest pain In 26 patients with arteriographically documented CAD 24 (92 %) demonstrated Tl[201] perfusion defects after symptom limited exercise testing. 2 patients, one with double and one with triple vessel diseae had normal Tl[201] scans both at rest and exercise. There were no apparent features to identify those patients with false negative tests from those in whom perfusion defects developed The high sensitivity in this study compared to other published data (1 15 21) may be in part, related to this study group since only a small proportion (5 of 20 patients) had triple vessel disease where failure to see a decrease in focal tracer uptake might be expected (18) The semi quantitative analysis of regional nuclide uptake may be another factor since this tended to reduce observer variation However this technique itself introduced inherent limitations since quantification of regional perfusion can only be relative and not absolute. The nuclide uptake in each anatomical area was compared to the zone with maximal uptake. This zone may have been better perfused than other areas but may well have been supplied by a significantly stenosed coronary vessel

The group of patients with normal coronary arteries or minor disease is small predominantly male and since the presenting symptom in each case was chest pain can scarcely be classed as "normal" Nevertheless, perfusion defects in Tl[201] exercise scintigraphy proved specific for the presence of CAD in all but one patient. This patient had a history of a typical chest pain a positive exercise test and an anteroseptal image defect both at rest and on exercise and may represent one of the group of patients with "angina" but normal coronary arteries (12, 14) Image data from the resting Tl[201] scan was less useful in predicting the presence or absence of CAD However blood flow and regional distribution abnormalities due to coronary artery stenosis of 50 % or more may only become apparent during exercise or pharmacological challenge (7 8) Hence since myocardial Tl[201] distribution parallels flow (22) Tl[201] scintigrams at rest may not detect haemodynamically significant CAD

The findings on the resting Tl[201] scan corresponded to LV wall motion on the ventriculogram. 10 of the 12 patients with perfusion defects at rest had corresponding areas impaired LV wall motion on the resting ventriculogram whilst 11 of the 13 patie with normal LV wall motion but signifi CAD had normal rest Tl[201] scans. This supports the conclusion from other data resting Tl[201] perfusion defects represent cardial infarction (9 17 23—24 26).

The exercise Tl[201] scintigram was in detecting the presence or absence of nary artery disease and the site of a perfusi defect corresponded to a diseased ves However prediction of individual cor stenosis from the exercise image was n possible. Regions supplied by vessels angiographically documented disease some instances did not develop perfusion fects, particularly in patients with triple sel disease. In others, the image defect c imply either RCA or LCx disease, or bo Several explanations can be proposed. anatomical distribution of vessels, whet right or left dominant, or balanced lation and the contribution of collateral cr culation may have affected the nuclide age. The development of ischaemia in on one of a number of potentially ischaem zones may have produced a Tl[201] scan unde estimating the extent of disease. As indicate above, the technique of analysis has limitations which will influence the final p diction of individual coronary lesions.

In conclusion these results indicate Tl[201] imaging was a useful non invasive nique in the investigation of patients w suspected coronary artery disease. Perfusi images after exercise were more sensitive detecting coronary artery disease than the rest image. The resting image to the presence or absence of impaired L wall motion. Perfusion defects on the Tl[201] scan tended to correspond to the d bution of vessel disease but prediction individual coronary disease from the findings was not possible.

11.

EFFECT OF DRUGS ON MYOCARDIAL PERFUSION SCANNING AND WALL MOTION IN PATIENTS WITH CORONARY INSUFFICIENCY

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potassium and cesium J NUCL MED 13 557 1972.
20 PROKOP E.K. STRAUSS H W SHAW J PITT B WAGNER H N Jr Comparison of regional myocardial perfusion determined by ionic potassium-43 to that determined by microspheres CIRC 50 978 1974
21 RITCHIE, J L., TROBAUGH G B., HAMILTON G W., GOULD K.L NARAHARA, K A. MURRAY J.A., WILLIAMS D L Myocardial imaging with Thallium 201 at rest and during exercise testing comparison with coronary arteriography and resting and stress electrocardiography CIRC 56 66 1977
22. STRAUSS H W HARRISON K., LANGAN J K. LEBOWITZ, E., PITT B Thallium 201 for myocardial imaging relation of Thallium 201 to regional myocardial perfusion CIRC. 51 641 1975
23 WACKERS F.J., TH., BECKER A.E., SAMSON G BUSEMANN SOKOLE, E. vd SCHOOT J B., VET A.J T M LIE, K.I., DURRER, D., WELLENS H Location and size of acute transmural myocardial infarction estimated from Thallium 201 scintiscans. CIRC 56 72, 1977
24 WACKERS F.J TH., BUSEMANN SOKOLE, E. SAMSON G vd SCHOOT J B., LIE K.I LIEM K.L., WELLENS H.J.J Value and limitation of Thallium 201 scintigraphy in the acute phse of myocardial infarction N E.J M 295 1 1976
25 WACKERS F.J TH DE JONG R.B.J Myocardial Imaging with Thallium 201 Medicamundi 21 103 1976
26 WACKERS F.J TH vd SCHOOT J B., BUSEMANN SOKOLE, E., SAMSON G., NIFTRIK, G.J C., DURRER, D., WELLENS H.J.J Non invasive visualisation of acute myocardial infarction in man with Thallium 201 BR HEART J 37 741 1976
27 ZARET B L STRAUSS H W., MARTIN N D WELLS H P Jr FLAMM M D Jr Non invasive regional myocardial perfusion with radioactive potassium Study of patients at rest, with exercise and during angina pectoris. N E.J M 288 809 1973

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The aim of any antianginal therapy is to relieve ischemia and possibly to restore compromised ventricular function We therefore investigated the effect of oxyfedrin a positively inotropic acting drug, a betablocking substance (Bupranolol) and a nitro compound on regional blood flow regional blood flow distribution and regional wall movement in a poststenotic asynergic myocardial region in patients with coronary heart disease We were interested to see the effect of the antianginal drugs on this poststenotic region and whether there was a correlation between local poststenotic blood flow and local wall movement.

METHODS

In 30 patients with the clinical diagnosis of coronary insufficiency who were subjected to coronary arteriography and laevocardiography the local poststenotic blood flow in the asynergic region was measured by the ^{133}Xe washout technique by means of a scintillation counter which was firmly placed over the chest when its location corresponded to the distal part of the left anterior ventricular wall The diameter of the collimator was 2,9 cm The blood flow distribution was obtained by slow injection of radioactive labelled micropheres (500 nCi ^{131}J 5 m Ci ^{99m}Tc) into the left coronary artery The scan was done one hour after the investigation in right oblique projection by means of a Gamma camera (1) Care was taken to collect as many counts as possible (ca 700 000 per projection) in order to get a good spatial resolution and scinti photo The distribution of perfusion in the asynergic region was evaluated as the percentage of radioactivity in this myocardial region as compared to the point of maximum activity Local wall movement out of the silhouette of the laevo was determined by drawing a short axis R^ perpendicular to the longditudinal axis of the left ventricle in the distal third of the left anterior ventricular wall in the asynergic region in RAP projection. The amount of the systolic shortening of this half axis R^ was taken as an index of local wall movement in the poststenotic region

The following hemodynamic data were recorded Heart rate, left ventricular enddiastolic pressure mean pressure in the aorta ejection fraction and circumferential fibre shortening velocity The substances were oxyfedrin (n = 10) Bupranolol (n = [illegible] and Isosorbiddinitrat, a long acting [illegible] compound (n = 10) The investigation [illegible] carried out in the following way

1 Recording of hemodynamic data, flow (^{133}Xe) blood flow distribution, wall movement (laevocardiogram).
2. Application of the drug (8 mg oxyf[illegible] i.v., 8 mg Bupranolol i v., 40 mg Iso[illegible] retard forte p.o)
3 Repeating of the above measurements [illegible]ter a definite hemodynamic effect of [illegible] drug could be observed.

RESULTS

1 The coronary arteriogram showed the [illegible]lowing findings
   a) Oxyfedrin group (n = 10) 5 pat[illegible] had more than 50 % stenosis of the [illegible] anterior descending artery (LAD), th[illegible] times before the branching off of [illegible] septal branch (proximal), twice distal In the other 5 patients the stenosis was l[illegible] than 50 % and four times located prox[illegible] to the first septal branch and once distal [illegible] it.
   b) Isosorbiddinitrat group (n = 10) [illegible]ven patients there was a proximal and one patient a distal stenosis of the LAD more than 50 % up to 90 % whereas [illegible] patients the stenosis was less than 50 [illegible]
   c) Bupranolol group Seven patients [illegible] a proximal stenosis of the LAD of [illegible] than 50 % and up to 90 % while in 5 [illegible]tients the lesions were less than 50 %.
2. The hemodynamic data before and [illegible] the application of the substances are [illegible]marized in Table I
3 Local blood flow The regional m[illegible]dial blood flow in the poststenotic [illegible] increased significantly in 7 out of 10 [illegible]tients under the positively inotropic act[illegible] oxyfedrin while no change or only a [illegible]nimal rise was observed in 3 patients ([illegible] 1). Regional flow increased in 5 out of [illegible] patients under isosorbiddinitrat. A [illegible]crease was observed twice and no [illegible] in 3 patients. Under betablockade a [illegible]cline in local flow was seen in 6 pat[illegible] a rise in 2 no change in 3 patients. [illegible] differences between the gropus were

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modynamic data (HR = Heart rate LVEDP = Left ventricular enddiastolic pressure, AOP = Mean ic pressure, EF = Ejection fraction, V_{CF} = Circumferential fibre shortening velocity), local stenotic flow and local wall motion in the poststenotic asynergic region (R^A) before and after 8 mg yfedrin i.v. 8 mg Bupranolol i.v. and 40 mg Iso-Mack retard forte p.o. The values given are the mean ue and the standard deviation of the mean value ($S_{\bar{x}}$).

	Oxyfedrin		Isosorbiddinitrat		Bupranolol	
	Before	After	Before	After	Before	After
r min.)	70.0 ± 2.9	77.6 ± 3.9	80.4 ± 4.4	77.4 ± 2.6	81.3 ± 2.4	71.0 ± 1.8
p	< 0.05		n.s.		< 0.001	
EDP m Hg)	13.6 ± 1.6	18.9 ± 1.4	20.4 ± 1.4	11.8 ± 1.5	12.3 ± 2.0	15.1 ± 1.4
p	< 0.01		< 0.001		< 0.01	
OP m Hg)	100.8 ± 5.3	104.9 ± 6.6	107.4 ± 6.7	96.6 ± 5.4	100.4 ± 3.6	102.5 ± 3.3
p	n.s.		< 0.05		n.s.	
)	57.4 ± 3.2	66.5 ± 4.8	–	–	62.5 ± 5.0	54.. ± 3.9
p	n.s.		–		< 0.01	
r circum/ s⁻¹)	1.13 ± 0.09	1.48 ± 0.09	–	–	1.18 ± 0.18	0.95 ± 0.11
p	< 0.01		–		< 0.05	
ow l/100g/ n)	38.3 ± 2.9	54.1 ± 6.4	52.8 ± 4.3	59.6 ± 2.7	55.8 ± 3.5	49.6 ± 4.1
p	< 0.05		n.s.		n.s.	
)	23.4 ± 3.3	39.2 ± 2.5	14.3 ± 4.0	28.9 ± 4.2	24.5 ± 2.2	15.6 ± 2.8
p	< 0.01		< 0.05		< 0.01	

ever not significant (Fig. 2) in either the nitro group or the betablocker group
Local blood flow distribution A significant redistribution into the poststenotic region was seen in 6 patients under oxyfedrin, (Fig. 3) in 5 under beta-receptor blockade and in 5 under isosorbiddinitrat. This redistribution was combined with an increase in local blood flow in 5 out of 6 patients under oxyfedrin, in the 5 under isosorbiddinitrat and in no patient under B-blockade.

4 Local wall motion The poststenotic wall motion improved significantly in both the oxyfedrin and isosorbiddinitrat group with 7 and 4 patients respectively normalizing the systolic shortening of the half axis in the asynergic region. On the contrary in the betareceptor blocking group 8 deteriorated and 2 stayed unchanged.

The aim of any antianginal therapy is to relieve ischemia and possibly to restore compromised ventricular function We therefore investigated the effect of oxyfedrin a positively inotropic acting drug, a betablocking substance (Bupranolol) and a nitro compound on regional blood flow regional blood flow distribution and regional wall movement in a poststenotic asynergic myocardial region in patients with coronary heart disease. We were interested to see the effect of the antianginal drugs on this poststenotic region and whether there was a correlation between local poststenotic blood flow and local wall movement.

METHODS

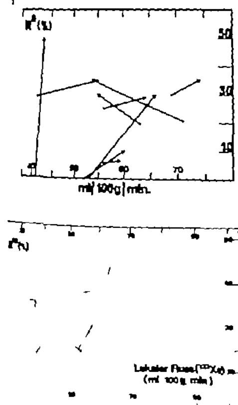
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4 Regional poststenotic blood flow (abscissa) and regional poststenotic wall motion (ordinate) before and after Isosorbiddinitrat (4a) and before and after oxyfedrin (b)

...red in 2 patients under beta-blockade could be due to the special situation where the oxygen requiring effect of an increased left ventricular diastolic wall tension is not offset by the oxygen saving effect of a decreased frequency and a reduced contractility (2). An increase in local blood flow and an improved wall motion was under isosorbiddinitrat and oxyfedrin usually combined with a shift of blood flow into the poststenotic region which can be interpreted as recruitment of the coronary flow reserve within the viable myocardium in the poststenotic region. It was only under beta-blockade where no correlation between flow and flow distribution existed. The finding of a redistribution of blood – flow into the poststenotic asynergic region in 5 patients under beta blockade is compatible with animal experiments in the chronically ischemic myocardium (4). It shows furthermore the additional information which can be gained by the perfusion scintigram. A parallelism between an improved perfusion and an enhanced wall motion was above all seen under oxyfedrin when the increase in contractility induced a rise in blood flow This parallelism was only present in half of the patients under isosorbiddinitrat and in no patient under beta blockade. Under a nitrocompound the local wall motion seems to be dependent both on a decrease of preload and afterload (3) and on an increase in local blood flow (2) whereby the interaction between these 2 factors varies from patient to patient.

That most probably hemodynamic factors or the state of contractility play a greater role in the poststenotic wall motion than blood flow is underlined by the finding of an impaired local wall movement under beta blockade despite a redistribution of blood flow into the poststenotic myocardial region in 5 patients or an increase in blood flow in another 2 cases.

SUMMARY

1 There are several groups of drugs which can be of use in patients with coronary heart disease.
2. The therapeutic effect of nitrocompounds is due to both a decrease in pre and after load as well as an increase in local poststenotic blood flow with a concomitant improvement in local wall movement in the asynergic region. Betareceptorblockers always increase the degree of asynergy in the poststenotic region which in combination with a reduction of frequency and contractility is an oxygen saving effect.
3 The relation between regional poststenotic blood flow and wall motion under therapy is unpredictable and varies as much with different drugs as among patients.
4 Unless one has extensive, invasively obtained information on a patient, which, however is not feasible in most cases, the therapy is always a trial and error procedure. It is for this reason that it seems to be sensible to combine drugs of different action like nitro-compounds and beta receptorblockers.
5 In some patients with coronary heart disease the therapeutic goal can be achieved not only by oxygen saving drugs but also by a positively inotropic acting substance.

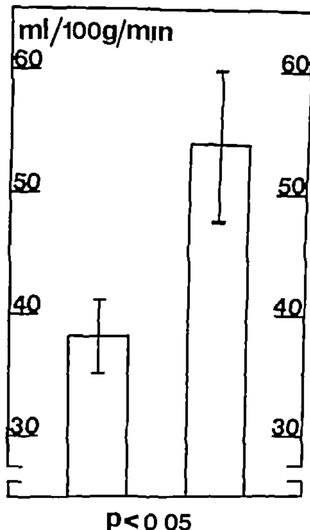


Fig 1 Regional poststenotic blood flow before (first column) and after (second column) 8 mg oxyfedrin i v



Fig 3 Regional poststenotic flow distribution befo (3a) and after (3b) oxyfedrin The perfusion gra in the distal part of the left anterior ventricul (arrow) is almost abolished after the drug Besid the size of the ventricle has decreased as cons quence of the increased contractility under oxyf drin The scans were taken in anterior— projection

5 Local blood flow and local wall mov ment in the asynergic region A paralle ism between an increase in blood flow an improved wall movement was seen the oxyfedrin group in 7 out of the patients and in the nitrocompound in half of the patients (Fig. 4). Under receptor blockade there was a striking parity between flow and wall motion decrease in flow being combined with change in the local contractile pattern or decrease in the systolic shortening ring despite an increase in flow

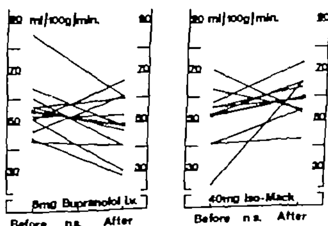
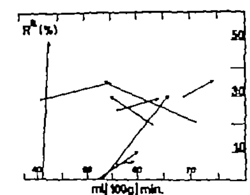
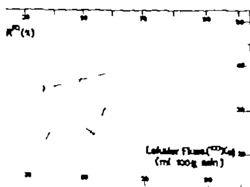


Fig 2 Regional poststenotic blood flow before and after Bupranolol (left side) and before and after Isosorbiddinitrat (right side)

DISCUSSION

The results show that substances of diff chemical structure can influence local blo flow in a poststenotic asynergic myocardia region. The most pronounced effect was under the positively inotropic acting o drin most probably as the result of an crease in contractility The rise in flow was seen under Isosorbiddinitrat was wi one exception concomitant with a decrease pre- and afterload whereby the decreased ing pressure in the left ventricle could en hance local flow via a diminished extravascu lar coronary resistance. The decrease poststenotic blood flow which occurred u der beta blockade can be explained by reduction in frequency and contractility The rise in local blood flow however which





g 4 Regional poststenotic blood flow (abscissa) id regional poststenotic wall motion (ordinate) before and after Isosorbiddinitrat (4a) and before and ter oxyfedrin (b)

ırred in 2 patients under beta-blockade ıuld be due to the special situation where e oxygen requiring effect of an increased ft ventricular diastolic wall tension is not fset by the oxygen saving effect of a de eased frequency and a reduced contractil

(2). An increase in local blood flow and an ıproved wall motion was under isosorbid nitrat and oxyfedrin usually combined with shift of blood flow into the poststenotic gion which can be interpreted as re uitment of the coronary flow reserve within e viable myocardium in the poststenotic gion. It was only under beta-blockade here no correlation between flow and flow stribution existed. The finding of a redist ution of blood – flow into the poststenotic ynergic region in 5 patients under beta- ockade is compatible with animal expe- nents in the chronically ischemic myocar um (4). It shows furthermore the additional formation which can be gained by the per sion scintigram. A parallelism between an improved perfusion and an enhanced wall motion was above all seen under oxyfedrin when the increase in contractility induced a rise in blood flow This parallelism was only present in half of the patients under isosor biddinitrat and in no patient under beta blockade. Under a nitrocompound the local wall motion seems to be dependent both on a decrease of preload and afterload (3) and on an increase in local blood flow (2) whereby the interaction between these 2 factors varies from patient to patient.

That most probably hemodynamic factors or the state of contractility play a greater role in the poststenotic wall motion than blood flow is underlined by the finding of an im paired local wall movement under beta blockade despite a redistribution of blood flow into the poststenotic myocardial region in 5 patients or an increase in blood flow in another 2 cases.

SUMMARY

1 There are several groups of drugs which can be of use in patients with coronary heart disease.
2. The therapeutic effect of nitrocompounds is due to both a decrease in pre- and after load as well as an increase in local poststenotic blood flow with a concomitant im provement in local wall movement in the asynergic region. Betareceptorblockers al ways increase the degree of asynergy in the poststenotic region which in combination with a reduction of frequency and contrac tility is an oxygen saving effect.
3 The relation between regional poststenotic blood flow and wall motion under therapy is unpredictable and varies as much with different drugs as among patients.
4 Unless one has extensive, invasively ob tained information on a patient, which, however is not feasible in most cases, the therapy is always a trial and error proce dure. It is for this reason that it seems to be sensible to combine drugs of different ac tion like nitro-compounds and beta recep- torblockers.
5 In some patients with coronary heart dis- ease the therapeutic goal can be achieved not only by oxygen saving drugs but also by a positively inotropic acting substance.

ACKNOWLEDGEMENT

The technical assistence of Miss Kahler Mrs. Ruttorf and Miss Wolski and the the secrete rial work of Mrs. Butzky are gratefully ac knowledged.

REFERENCES

FELIX, R., W PENSKY P THURN J WAGNER, C. WINKLER Selektives Koronarogramm und koronares Perfusions-Szintigramm.
I. Normale Perfusionsverhältnisse.
Fortschr Röntgenstr 120 513 (1974).

FLECK, E., J DIRSCHINGER, C. LORACHER, A. REDL, W RUDOLPH Vergleichende Untersuchungen über die Wirkung verschiedener Nitrate auf die regionale Myokarddurchblutung bei Patienten mit koronarer Herzerkrankung.
Zschr Kardiol. Suppl 3 87 (1976).

LICHTLEN P., HJ ENGEL.
Coronary dynamics of various antianginal drugs at rest and during exercise measured by the precordial Xenon residue detection technique.
In Coronary Angiography and Angina pectoris.
Georg Thieme, Stuttgart 1976 S. 365

VATNER, S.F., H BAIG H.R. OCHS T.W MAUDERS, M PAGANI
Effects of propranolol on regional myocardial function electrocardiograms and blood flow in conscious dogs with myocardial ischemia.
J Clin. Invest., in press.

ence

MEXILETINE EFFECT ON MONOPHASIC ACTION POTENTIAL (MAP) OF RIGHT VENTRICLE IN MAN

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ICTORIA Australia

In the analyses of single ventricular ectopic beats during acute myocardial infarction the interest has mainly been focused upon the time relation between the start of the ectopic beat and the repolarization of the preceding beat. However apparently identical premature ventricular ectopic beats may or may not result in repetitive ventricular dysrhythmias Therefore the refractory state after the ectopic beat must be of equal interest as the excitation process of that beat.

We have therefore aimed to study the repolarization as well as the propagation of induced ectopic ventricular beats and the influence of Mexiletine, an antiarrhythmic drug with electrophysiological properties similar to Lignocaine (1 2, 3 10)

MATERIAL AND METHODS

The study was performed on 9 healthy male volunteers. It was presented for and approved by the Ethical Committee of the hospital

By means of a percutaneously introduced disposable suction electrode catheter* the monophasic action potential (MAP) was recorded from the outflow tract of the right ventricle (4) In addition a bipolar pace[illegible] catheter was placed at the apex of the ventricle for programmed ventricular pa[illegible] (5) The effective refractory period of the [illegible]tricle was determined via the pacemak[illegible] theter with a precision of 2 msec. The [illegible]cle was then paced with a regular basic [illegible] length of 600 or 500 msec. Premature st[illegible] were thereafter introduced every 8th to [illegible] beat in such a way that basic cycle [illegible] scanned with ectopic stimuli from the [illegible] value of the effective ventricular refrac[illegible] period up to the basic cycle length. [illegible] the refractory period the premature sti[illegible] were given with increments of 5 msec. MAP was recorded continuously during programmed ventricular pacing. The [illegible]grammed ventricular pacing with MAP [illegible]cording was then repeated in the same [illegible] described above 10 min after a slow bo[illegible] injection of 2 mg Mexiletine/kg BW

Precordial ECG pacemaker signal MAP and RV electrogram were recorded [illegible] tape. The records were then replayed [illegible] analysed with respect to the parameters [illegible]monstrated in fig. 1 and 2. The time from [illegible] pacemaker stimulus of the last basic pa[illegible] beat to the onset of depolarization of the [illegible]

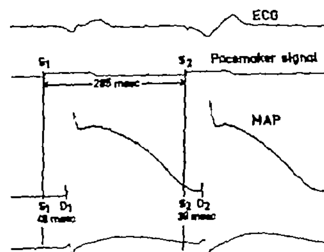


Fig 1 Example of MAP recording and time interval calculation From top to bottom Precordial ECG pacemaker signal, MAP signal right ventricular electrogram
S_1 – regular pacemaker stimulus S_2 – premature pacemaker stimulus D_1 – Start of depolarization of MAP during regular pacing D_2 – Start of depolarization of MAP during ectopic beat

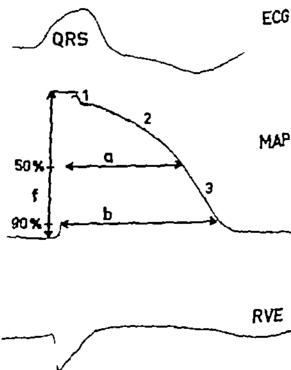


Fig 2 Map recording from subject no 7 to sh[illegible] relationship between the MAP signal to ECG a[illegible] right ventricular electrogram The duration of [illegible] MAP is indicated at the level of 50 and 90 % [illegible] repolarization

---

*ABO Trading, Tullv., 1138 S-430 41 Kullavik, Sweden.

ular MAP (S_1-D_1) C = basic conduction ...e) was measured as well as the corre ...onding interval of the early ectopic beat ...$-D_2$). The measures were then related to ...e value of the basic cycle length (S_1-S_1) ...d the premature interval (S_1-S_2). In this ...ry we analysed the conduction of all pre...ature beats as well as the conduction during ...gular pacing.

For assessment of *repolarization* during ec...topic beats, the duration of the MAP was ...easured at the level of 90 % repolarization. ...he same analysis was also done from re...ords during the regular pacing.

...ESULTS

...onduction

...he conduction time of the early ectopic ...eat, S_1-D_2, is related to the prematurity of ...he ectopic impulse S_1-S_2, in a characteris...ic way (fig 3 and table I). Close to the refrac...ory period, the time from right ventricular ...pical stimulation to outflow tract excitation ...s substantially longer than that during the ...asic paced beat. There is also a period when ...he conduction time is significantly shorter ...han that of the basic paced beat – phase of ...ccelerated impulse propagation

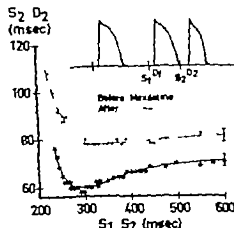


Fig 3 Effect of coupling interval and of Mexiletine upon conduction of ectopic impulses from pacemaker electrode in apical position in right ventricle to outflow tract of right ventricle

Repolarization

The duration of the MAP of the early ectopic beat is markedly affected by the prematurity of the beat, e.g. the preceding cycle length (fig 4 and table I). The duration measured at 90 % repolarization of beats close to the refractory period is approximately 40 msec shorter than that of the basic paced beat.

Table I

...ffect of Mexiletine upon Conduction and Repolarization during Regular Pacing and during Etopic ...eats (All Values in msec).

...se no.	Analyses during regular pacing				Analyses of earliest excited ectopic beat				Analyses of "super normal" beat	
	S_1-D_1	2 sd			$(S_2$-$D_2)$max		MAP-duration at 90 % repolarization		$(S_2$ $D_2)$min	
	C		M		C	M	C	M	C	M
	39	4.0	46	2.1	44	64	198	208	32	46
	57	3.4	71	2.2	68	92	196	200	50	64
	67	2.3	81	2.4	82	118	174	185	56	78
	48	1.8	51	2.0	50	60	180	190	38	50
	72	4.0	80	5.0	106	116	188	198	64	70
	81	4.4	89	3.6	106	116	200	212	72	86
	79	4.8	79	2.4	96	96	176	210	74	76
	37	2.4	45	3.1	36	50	200	218	32	42
...ean	59		66		71	85	194	205	51	62
...ifference	$p<0.01$				$p<0.01$		$p<0.01$		$p<0.01$	

...bbreviations C = control values before mexiletine. M = values after mexiletine.
...ther abbreviations see text.

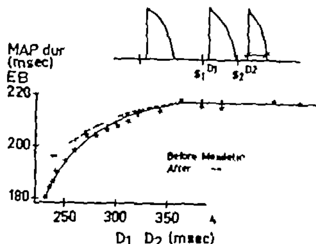


Fig 4 Effect of prematurity and of Mexiletine upon duration of MAP of early ectopic beats

Mexiletine

The *conduction* of the early ectopic beat is markedly influenced by the drug (fig 3 and table I) The accelerated propagation of the ectopic beat is almost completely abolished and the delay of the earliest ectopic beat is more pronounced than before the drug was given In addition the basic conduction time is slightly prolonged All these effects are statistically significant.

Repolarization is also affected by Mexiletine The shortening of the MAP of the early beats is thus much less pronounced than before the drug was given (fig 4 and table I) Again this is highly significant. The difference looses its significance when the $D_1 - D_2$ value amounts to more than 50 msec. over the value of the refractory period. During regular pacing the MAP duration is unaffected by the drug.

DISCUSSION

The present investigation has demonstrated several findings that may be of importance for the antiarrhythmic action of Mexiletine. The conduction of the impulse from the apex to the outflow tract of the right ventricle is delayed during regular rhythm. This decreased conduction velocity is likely to be due to the decreased maximal rate of rise of depolarization of myocardial cells caused for Mexiletine (3). This influence upon maximal depolarization rate is an effect noted for several anti arrhythmic drugs (6)

The rate of rise of an action potential is strictly dependent upon the actual membrane polarization (7) Therefore the rate of an action potential will be decreased elicited during the repolarization phas preceding action potential This is ably the explanation why the conduc the impulses close to the refractory prolonged compared with that of the paced beat. The mechanism of this tion delay has been more extensively sed elsewhere (8) The exaggeration conduction impairment of early ectopic caused by Mexiletine may be another of importance for its antiarrhythmic m action This has been more extensivel cussed elsewhere (8).

The influence upon the supernc phase conduction of ectopic beats is nounced than the effect on the conducti the very early ectopic beats. A probable trophysiological explanation for the normal phase is that the signal passes cells with early phase 4 e.g. purkinjecells. As these have a high brane polarization at the moment of tation, the rate of rise of the action pote will be increased and thereby also most l the conduction velocity (9). The effec Mexiletine has been studied upon the ac potentials of the cells of the specialized ductive system that most likely lim tive refractory period in the way estimate this study (3) It is, however difficult to plain the influence of Mexiletine upon supernormal conduction from these stu A slight action potential shortening has observed elsewhere (3). The effect of Mex tine upon the repolarization of the early e pic beats is however a new finding. Ne has this effect been described in literatur an effect of any other antiarrhythmic dru perhaps due to the fact that enough has not been focused upon the repolarizat of early ectopic beats.

Another class of antiarrhythmic drugs however delay ventricular muscle repol zation already during regular rhythm (6). I therefore tempting to believe that even t effect may play a role in the anti arrhythm mechanism of Mexiletine.

Conduction and repolarization-effects Mexiletine upon early ectopic beats bo cause a delay of repolarization after ear ectopic impulses. The time after an early e topic impulse when an apart from sup

part of the myocardium reaches exitability — and thereby vulnerability — will thus be substantially delayed by Mexiletine. It may be speculated that these effects are active also upon concealed impulses, thereby facilitating the antiarrhythmic activity of Mexiletine.

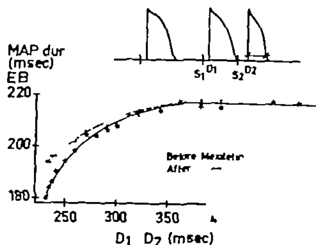


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Conduction and repolarization-effects of Mexiletine upon early ectopic beats both cause a delay of repolarization after early ectopic impulses. *The time after an early ectopic impulse when an apart from stimulus*

REFERENCES

1 ALLEN J D & ARNOLD J M O Comparison of the effects of mexiletine lignocaine and procaine amide o canine purkinje fibres. J Physiol 236 26A 1974

2. SINGH B N & VAUGHAN WILLIAMS D M Investigations of the mode of action of a new antidysrhythmic drug KO 11734 Brit J Pharmacol 44 1 1972

3 VAUGHAN WILLIAMS E.M Mexiletine in isolated tissue models. Postgraduate Medical Journal 53 (suppl 1) 30—34 1977

4 OLSSON S B VARNAUSKAS E., KORSGREN M Further improved methods for measuring monophasic action potentials of the intact heart. J Electrocardiol 4 19 1971

5 OLSSON B., BRORSSON L., HARPER, R. & RYDÉN L. Estimation of ventricular refractoriness in man by the extra stimulus method. Cardiovascular Research volume XI 31—38 1977

6 VAUGHAN WILLIAMS E.M Classification of antidysrhythmic drugs. Pharmacology and Therapeutics B 1 115—138 Pergamon 1975

7 JOSEPHSON M E., CARACTA, A.R. LAN S H GALLAGHER J.J & DAMATO A.N Effect of lidocaine on refractory periods in man. American Heart Journal 84 778—796 1972.

8 HARPER, R.W & OLSSON S B The effect of the coupling interval and mexiletine on the conduction of premature ventricular beats in man A study using monophasic action potential recordings from the right ventricle. In manuscript.

9 HOFFMAN B F Physiological basis for disturbance of cardiac rhythm and conduction Prog Cardiovasc Dis 2 319 1963

10 HARPER, R.W., OLSSON S B & VARNAUSKAS E. Effect of mexiletine on monophasic action potentials recorded from the right ventricle in man. In manuscript.

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Supplementum 616

Survey of Serum Lipid Levels in Icelandic Men Aged 34-61 Years

An epidemiological and statistical evaluation

By
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Davíð Davíðsson
Ólafur Ólafsson
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Þorsteinn Þorsteinsson

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of the Icelandic Heart Association
Reykjavik Iceland

Survey of Serum Lipid Levels in Icelandic Men Aged 34-61 Years

An epidemiological and statistical evaluation

By
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Þorsteinn Þorsteinsson

CONTENTS

F O R E W O R D

This report from the Heart Preventive Clinic of the Icelandic Heart Association is one in a series of reports on a prospective health survey conducted in the Reykjavik area since 1967

The emphasis in these reports is on the publication of results and their chief statistical characteristics in the form of computer printed tables and graphs

They include detailed descriptions of the methods used in the health survey as well as various accompanying documents Discussion and references to other work is limited as the purpose of the report is primarily to publish detailed results in an accessible format

This report deals with a matter of special interest in cardiovascular epidemiology the blood lipids

Tables and figures in reports on the analysis of data from the Icelandic Heart Association s Health Survey in the Reykjavik area are labelled with a capital letter which refers to the stage of the survey a Roman numeral referring to the number of the report and an Arabic number which is the number of the table or figure in that report Thus Table A III 1 is the first table in the third report on the first stage of the survey

Thanks are due to Mr H Filippusson Ph D Dept of Clin Chem University Hospital Reykjavik for the translation of this report into English

We also acknowledge gratefully financial support from The Debt Collection Fund of Icelandic Banks which made this publication possible

Reykjavik October 1977

The Report Committee

HEALTH SURVEY IN THE REYKJAVIK AREA 1967 - 68

INTRODUCTION

In th autumn of 1967 the Icelandic Heart Association embarked on Stage I of an extensive health survey Approximately one-third of each of 16 age groups of men aged 34 to 61 years domiciled in the Reykjavik area were invited to participate in Stage I which was almost completed by the autumn of 1968 [1]

The primary aim of the health survey which is a prospective study is

1) to detect cardiovascular and various other diseases in their arly stages to find th preval nce and incid nce of these di eases as well as their causes in search of pr ventive measures

2) to ass ss the financial and h alth ben fits to be gained from such mass screening programs

To achieve these aims Stage I of the male survey included a st dy by means of a questionnaire of the medical and social h story of the participants heart and lung X ray spirometry el trocardiogr phy ey tonometry measurement of blood pressure height and weight as well a some measurem nts on bones and skin f ld thi kn ss a glucose tol ranc test blood and urine analyse and a medical ex mination

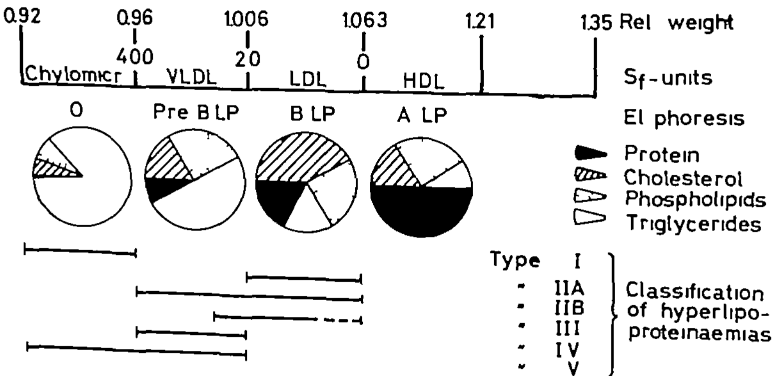


Figure A III, 1 T p S paratio f s rum lipoprot in by ultra ntrifugation and le trophoresis
Middl Approximat percent g compo ition of th main lipoprotein fr cti n
Bottom Cl sifi ti n f hyperlipida mias ccording to Fredricks n and Le

Diseases of the coronary and other arteries often occur with other diseases such as diabetes diseases of the kidney diseases of the thyroid and others Elevated concentrations of cholesterol and various other lipids commonly occur with these diseases as well as fatty deposits in the walls of blood vessels and elsewhere in the body

Chemical analyses of fatty deposits in the walls of blood vessels from patients with the diseases referred to above have shown them to be rich in cholesterol as well as other lipids showing various stag s of calcification

Most of the cholesterol in blood is together with phospho lipids and triglycerides bound to proteins in so called lipoprot ins

Ultracentrifugation can be employed to classify lipoproteins according to th ir sedimentation behaviour which is measured in o called Svedberg flotation units (S_f) The different sub classes are identified by their respective S_f values

Lipoproteins have also been classified according to their electrophoretic mobilities Thus the lipoproteins have been di id d into the following main classes Chylomicrons pre-β lipoprot ins β lipoproteins and α lipoproteins By methods based on this principle v rious types of hyperlipoproteinaemias have be ind ntified Fig 1 shows the classification of lipoproteins c ording to the above mentioned methods and their interrelation r ps as well as the major types of hyperlipoproteinaemias r a t ris d by elevat on of th various classes of blood lipo- prot n [2]

.o studi have indic ted that for males und r the age of 0 y a th re is a clo er association of coronary diseases with t E d ich serum β lipoprot ins (S_f 20 400) than with n l st rol i h s rum β lipoproteins ($_f$ 0 12) [3] [4]

f ll th blood lipids cholest rol ha been most thoroughly t g t d ince it is most asily det rmired wh rea until rt y o ly very fe laboratorie had at their disposal the

techniques necessary to thoroughly study the various other lipids

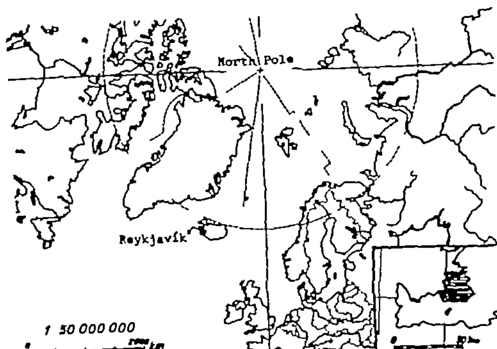
Even though it is considered proven that high concentrations of cholesterol and various other lipids in serum are risk factors the problem of the biological connectior remains unsolved

In addition to much experimentation with animals a large number of health surveys have been carried out in the last two decades in order to throw light on this problem In the United States and in various European countries these have been follow-up studies aimed among other things at investigating the development of cardiovascular diseases in people with different living habits These studies have cast some doubt on the importance of various known risk factors for cardiovascular diseases such as cigarette smoking and body fatness [5]

These studies will not be further elaborated on here except to point out that health surveys show up variations from one nation to another in the numerical characteristics for serum cholesterol concentration The results of surveys carried out in other countries cannot lead to any definite conclusions about the concentration of cholesterol in the serum of Icelanders [6]

No systematic investigations of lipids in the human body have been carried out in this country except for a study of the effect of cod liver oil administration on serum cholesterol concentration in elderly people That study did however indicate that Icelanders were among those nations with the highest cholesterol concentration [7]

The subject of this report is the measurement of serum concentrations of β lipoproteins cholesterol and triglycerides The main emphasis is on the distribution of these values and their main statistical characteristics e g mean values standard deviations and several fractiles



METHODS

Pop lation.

I l d is a volcani island in the North Atl ntic Ocean close s th of th Arctic circle with an area of 103 000 sq km

In the years 1931 60 th me n monthly temperature in Reykja- v ri d between 3 8 C +3 2 C in the coldest month January d betw n 10 1 C 13 2 C in the warmest July Th mean annual urb r f rainy days (1 0 mm) w s 212 The mean annual number of h with b ight sunshine was in Jun 189 nd 8 in Dec [8]

A o ding to historical docum nts cel nd w s settled in the 9th d 10th c turi s AD mainly from Norway but also from The B t sh Isl

Anthropolog al tudies on skulls from the ti o o settl m nt an blood gro p in stigation f th pres nt inhabitants show a

Table A III 1

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Number of men invited to participate (participants) in each age-group - and the percentage of participants investigated

Birth -year	Age 1968	Particip invited N	Particip investigated Response N	%	%	Corrected response 1/ %
1907	61	128	87	68 0	68 0	69 6
1910	58	131	86	65 6	73 6	74 3
12	56	160	128	80 0		
1914	54	167	127	76 0	75 2	75 7
16	52	162	127	78 4		
17	51	172	125	72 7		
18	50	159	117	73 6		
1919	49	162	127	78 4	77 0	77 3
20	48	222	175	78 8		
21	47	225	173	76 9		
22	46	203	150	73 9		
1924	44	207	167	80 7	75 2	75 4
26	42	221	164	74 2		
28	40	225	160	71 1		
1931	37	212	149	70 3	70 3	71 3
1934	34	199	141	70 9	70 9	71 6
Total		2955	2204		74 6%	75 1%

1/ Calulated after exclusion of those who had emigrated or died from Dec 1 1966 to Nov 30 1967 according to the National Roster on Dec 1 1967

greater similarity to the Scottish and Irish people than to the candinavians [9] [10]

Iceland was a sovereign state but came under the Norwegian crown in 1262 and later under the Danish crown until it became a republic in 1944

Icelandic culture is essentially candinavian However for centuries there have been commercial and cultural relations with West European countries especially Britain [11]

The area s l cted for this survey lies on the south west coast of Ic land and includes the capital Reykjavik, and five of the neighbouring communes It lies within 11 kilometers from the Heart Preventive Clinic in Reykjavik where the investigation was performed

The e has been a considerable and fairly constant migration to th Reykja ik area in the first half of this century from all parts of the country In the year 1901 about 10% of the nation lived in th Reykjavik area compared to 60% in 1960 and 52% 1968

A computeri ed regist r The National Ro ter was establish d i 1953 bas d on th National Census of Dec 1st 19 0 and a pe l ns t ke on O t 16th 19 The National Roster is rro t d on Dec 1st ea h ye r

The tot l popul tion of Iceland was on Dec 1st 1967 about 200 000 At that time about 10% 000 w re living in the Reykjavik re [12]

Th le popul tio s l t d (participants) for the health s y ompri ed s xteen ge groups born respectively in 1907 10 1 14 16 17 18 19 20 1 22 24 26 28 31 nd 34 totalling approx 8500 r n [1]

I tage I one third of ach group was invited to attend t1 na ly tho born on th 1st th 7th 8th d 31st d y of e ch onth[1] Altogeth r there were 2956 male p rti p nt in tage I ged fr m 34 to 61 y ars

---

1 Each ge gro p wa divid d into three gro ps A B and C a rd ng to bi thdays Gro p B w in ited to participate in t ge I

Table A III 1

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Number of men invited to participate (participants) in each age-group - and the percentage of participants investigated

Birth -year	Age 1968	Particip invited N	Particip investigated Response N	%	%	Corrected response 1/ %
1907	61	128	87	68 0	68 0	69 6
1910	58	131	86	65 6	73 6	74 3
12	56	160	128	80 0		
1914	54	167	127	76 0	75 2	75 7
16	52	162	127	78 4		
17	51	172	125	72 7		
18	50	159	117	73 6		
1919	49	162	127	78 4	77 0	77 3
20	48	222	175	78 8		
21	47	225	173	76 9		
22	46	203	150	73 9		
1924	44	207	167	80 7	75 2	75 4
26	42	221	164	74 2		
28	40	225	160	71 1		
1931	37	212	149	70 3	70 3	71 3
1934	34	199	141	70 9	70 9	71 6
Total		2955	2203		74 6%	75 1%

1/ Calulated after exclusion of those who had emigrated or died from Dec 1 1966 to Nov 30 1967 according to the National Roster on Dec 1 1967

great r similarity to the Scottish and Irish people than to the Scandinavians [9] [10]

Iceland was a sovereign state but came under the Norwegian crown in 1262 and later under the Danish crown until it became a republic in 1944

Icelandic culture is ess ntially Scandinavian However for centuri s there have been commercial and cultural relations with W st European countries especially Britain [11]

The area selected for this survey lies on the south west coast of Iceland and includes the capital Reykjavik, and five of the neigh bouring commun s It lies within 11 kilometers from the Heart Preventive Clinic in Reykjavik where the investigation was performed

There has been a considerable and fairly constant migration to the Reykjavik area in th first half of this c ntury from all parts of the country In the year 1901 about 10% of the nati n lived in th Reykja ik area compared to 50% in 1960 and 52% 1968

A computerised register The National Roster was establish d in 1953 b ed on the National Census of D c 1st 19 0 and a pecial cen us taken on Oct 16th 19 2 The National Roster is c rre t d o D c 1 t e ch year

Th total popul tion of Iceland wa on Dec 1st 1967 about 200 000 At that time about 104 000 were living in th Reykjavik rea [12]

Th r le population el cted (participants) for the health survey apr d ixteen age-groups born respectively in 1907 10 12 14 16 17 18 19 20 21 22 24 26 28 31 and 34 totalling approx 8500 men [1]

I s I one third of ach group w s invited to attend t i arely tho born on the 1st 4th 7th 28th ar 31 t d y f ach month[1/] Altogeth r th re were 2955 male p t ipa ts in t g I aged from 34 to 61 y ars

---

1/ h ge gro p w s divided into thre groups A B and C a ding to bi thdays Gro p B was invit d to parti ipate i t g I

Table A III 2

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Marital status[1/] in each cohort of males (%) invited to participat
(participants) in the first stage of the survey - and percentage
of participants investigated (% response) in each subgroup

Cohort		Marital status								Total	
Age		Unmarried		Married		Widowers		Divorced Separated		%	N
61	% particip	21		70		5		4		100	12
	% response		37		79						
58 56	% particip	11		80		2		7		100	29
	% response		48		79						
54 52	% particip	18		76		2		5		101	66
51 50	% response		53		82						
49 48	% particip	13		81		1		5		100	81
47 46	% response		57		81						
44 42	% particip	14		81		0		5		100	65
40	% response		46		82						
37	% particip	17		76		1		6		100	212
	% response		39		80						
34	% particip	17		78		1		5		101	199
	% response		46		77						
Participants N		443		2327		31		153		2955	
Response %		49 2%		81 1%		62 5%		50 3%		74 6%	

1/ According to the National Roster Dec 1 1966

Response

In early November 1967 invitations were mailed to all partici pants wherein they were asked to indicate wh ther they were prepared to attend a health survey in search for cardiovascular dis ases sometime during the period from November 1967 to June 1968

The letter of invitation stated that the survey was free and included an outline of what it involved

The survey was publicized through newspapers and radio

A second invitation identical to the first one was in March 1968 mailed to those who had not yet replied to the first one

Altogether 96% of those who had accepted the first or the second in itations did attend the clinic This corresponded to some 68% of all participants

From Aug t to November 1968 about two-thirds of those who had not replied to either invitation were contact d by telephone In this way some 6% of the participants w re persuaded to attend

Duri g May and June 1969 a few men were contacted by tele phon and about 2% of the participants subsequently attended the linic

The clinic did not organize any transport for the participants to or from th clinic nor did it pay any expenses in curred in this re pect

Th low st e pon in individual ag groups was 58% among th 61 yea old males and the highest 81% among 44 year old l If th ag groups are pool d into 5 year cohorts 30 34 y rs ld 35 39 y ar old et th response rate is highest 77% ong 45 49 ye r old male but tends to be low st in the y ung t nd th ldest age groups The ov rall response rate a 74 6% r 2203 parti ipants Discounting those participants wh or migr t d before Dec 1st 1967 the lowest re po r t one cohort i 70% and the overall respon 75 1% b t none of tho ho died had previously attended ror had any

of those who had emigrated Further information on attendance can be seen in Table A III 1 page 8

Non-response

The religion and marital status of all participants are known Some 83% of the males invited to participate in Stage I belonged to the National Church (Lutheran) according to the National Roster on Dec 1st 1966 some 10% belonged to Free Churches and some 6% belonged to no religious sect Attendance in individual age groups seems independent of religious affiliation

As regards marital status the situation is different Some 81% of married men attended the clinic whereas attendances among unmarried men and divorced men were similar or about 50% Further information on attendance with respect to marital status can be seen in Table A III 2

Collection of blood samples

From November 1967 to June 1968 about 20 men were systematically given an appointment to attend the clinic each weekday These were issued by letter some 10 days in advance to men who had accepted an invitation The appointments were arranged in such a way that as far as possible all age groups would be equivalent with respect to time of day weekday and time of year on which the appointments were given 1/ [1]

Participants were instructed not to eat or drink after 22^{00} hrs on the night before their visit to the clinic If a participant had not fasted for the required period of time he was asked to come again later to give a blood sample

Blood samples were collected between 8^{30} hrs and 10^{30} hrs The participant lay down on a couch where an electrocardiogram was taken and blood pressure measured This took some 3 minutes After this the cuff of the sphygmomanometer was reinflated to compress the veins A nurse then collected blood from an arm vein into three Vacutainer B-D tubes (Beckton Dickinson & Co

1/ This refers to the first visit to the clinic but participants were expected to reattend the clinic some 10 days after the first visit

U S A) The tubes were sufficiently air-evacuated to draw 4-5 ml of blood into the first two tubes and about 15 ml into the third (The blood lipid analyses were done on blood from the last tube) Blood sampling took 1 2 minutes

Chemi l analyses

Blood samples reached the laboratory before noon and soon after that separation of serum commenced For this the samples were centrifuged for 10 minutes at 2000 2200 r p m (1000 G) in a HSE uper Medium centrifuge Occasionally further centrifugation was n eded for ad quat separation On the other hand nothing was done about haemolysis Subs qu ntly 2 7 ml serum w re decanted into 10 15 ml test tubes When serum was poorly separated the transfer was don by m an of a Pasteur pipette inst ad of decantation The tub s were then stored in a re frigerator at approximat ly 4 C with aluminium foil covering th row of tub s

Beta lipoprotein in s rum w re determined after precipita tio with antis rum Antihuman Beta Lipoprotein Precipitin S rum obtained from Hyland Laboratories Los Angeles The prec pitat on was carri d o t by mixing one drop of erum with two drop of antis rum on a plastic oated card The mixture was ub quently drawn into glass capillaries which were then sealed in a g s flame The precipitate was spun down in the capillary in an Adams Autocrit Haematocrit entrifuge at 12500 r p m for 5 min (15 500 G) The depth of th pre ipitate was th n me red on mm le with th aid of a magnifying glass to an ac ura y of 0 1 mm

Th quipment sed for the determination with th exception of th ce tr fug w s btain d from Hyland Laboratorie and the omp y ng dire tio were follow d precisely (See Appendix pag 144)

Triglyc rid s were d termin d fluorimetric lly ac ording to th proced re of Kessler and Led rer [13] This semiautomatic tr d n olv s saponification of triglycerides in an isopropanol

extract The subsequent oxidation of glycerol leads to the formation of formaldehyde which reacts with ammonia and acetylacetone to form a fluorescent compound 3 5 - diacetyl - 1 4 - dihydrolutidine The excitation wavelength was 405 nm and the fluorescence was measured at 480 nm

Extraction was carried out after noon on the day blood samples were centrifuged The time which elapsed from collection of the first blood sample until extraction had been completed could be up to 7 hours

A Folin pipette was used to transfer 0 5 ml of serum into 9 5 ml of isopropanol which had been dispensed by means of an Exelo automatic pipette The tube was gently agitated with a Vortex mixer closed with a screw cap containing a teflon sealing disc and then shaken vigorously for about 15 seconds this length of time being estimated by counting to 15 Culture tubes 16 x 125 mm were used

The closed tubes were subsequently allowed to stand in a tube rack for at least 20 min (20-60 min) Some 2 g of zeolite mixture were then dispensed into each tube and the tube rack shaken vigorously several times by hand whereupon it was left with the tubes closed at room temperature overnight Every other day the tubes had to wait 24 hours longer and occasionally 2-3 days longer due to holidays

The tubes were centrifuged early in the morning at 2000 - 2200 r p m (1000 G) for 10 minutes

Reagents used for the triglyceride determination were as follows

Isopropanol (Isopropyl Alcohol Shell Chemicals See Appendix page 143) was obtained from the Government Pharmaceuticals Dept in drums containing 5 imp gallons

When needed some 4 5 litre of the isopropanol were shaken with 0 05-0 10 g of sodium borohydride (zur synthese kat no 6373 *E Merck AG Darmstadt) to remove aldehydes and* the mixture was subsequently distilled from a 5 litre flask at 82 83 C in an all glass apparatus

The redistilled isopropanol was stored in a 4 5 litre flask

and lasted up to one month No special test for aldehydes was carri d out after distillation

The zeolite mixture served to remove phospholipids and glucose which interfere with the triglyc ride determinations

The zeolite mixture was prepared by crushing 500 600 grams of zeolite (W Z T ylor Co Baltimore Md USA) in a Waring Blendor followed by drying for 4 hrs at 110 C in an oven To 100 parts (by weight) of the dried zeolit were added with thorough mixing 10 parts of Lloyd s Reagent (Hartman Leddon Co Philadelphia USA) 10 parts calcium hydroxide ($Ca(OH)_2$ pro ana lysi, E Merck AG Darmstadt Germany) and 2 7 parts of copper sulphate ($CuSO_4$ $5H_2O$ pro analysi E Merck AG Darmstadt Germany)

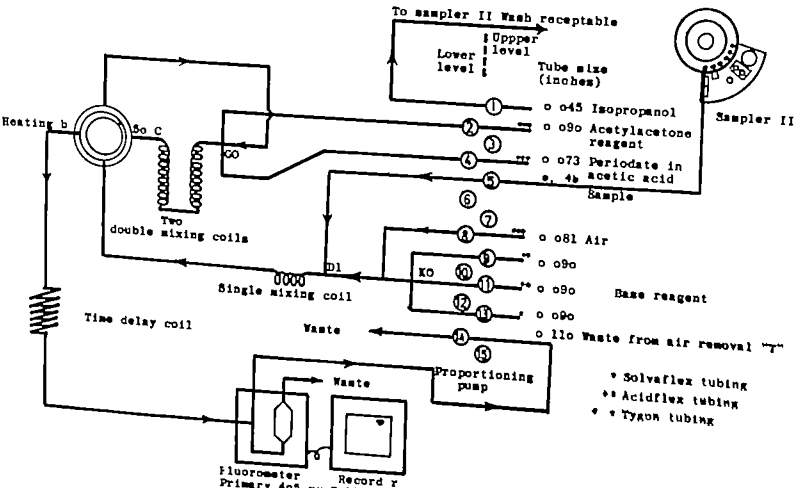
Prior to each run i e analyses of triglyc rides on the AutoAnalyzer three reagents were prepared

Th bas reagent was prepared as follows: 6 g potassium hydroxide (P 248 u s p pellets Fischer Scientific Co and Eimer and Amend USA) were weighed out on a top loading balance dissolved in 250 ml of deionized water and mixed with 750 ml of sopropanol

The sodium metaperiodate reage t was prepared as follows 2 13 g of sodium metaperiodate ($NaJO_4$ MW 213 89 zur Bestimmung vic Hydroxylgruppen E Merck AG Darmstadt Germany) were we gh d out on a top loading balance and dissolved in 46 6 ml (in th mea urement the last digit was e timated) of acetic acid pro analysi (100%) E Merck AG Darmstadt Germany) and 354 6 ml f d ionized w t r Th mixture was stirred with a glass rod until the constituent had dissolved

The acetylacetone reagents was prepared as follows 10 ml i opropanol and 3 ml ac tyl aceton ($CH_3COCH_2COCH_3$ rein MW 100 12 E Merck AG Darmstadt Germany) w re measured out by me n of graduated pipette and mixed by haking 400 ml of an ammonium cetat solution pH 5 8 6 2 w re then added The ammonium ac tate s lution was prepared by first mixing 0 5 ml d on z d w t r with 228 ml of a etic acid (a s above) in a 2 litre brown screw cap bottle and then adding 290 ml of 25% ammonia

TRIGLYCERIDES



Fluorometer Primary 4o5 mμ B &L interference filter secondary 3 71 Co ni g filter

Figure A III 2 health survey in the Reykjavik area Stage I 1967 - 68 - Men
AutoAralyzer flow diagram for the determination of serum triglycerides

(E Merck AG Darmstadt Germany) The mixture was allowed to cool and was th n diluted to the 2 litre mark on the bottle with d ionized water The pH of this solution was checked before use The ammonium acetate solution was sufficient for several runs

Deionized water was prepared by passing tap water through an ion ex hange resin b d in an Elgastat apparatus (Type C 203)

tandards w re prepared from triolein redest (purum Fluka AG Buchs Switzerland) which was obtained in 50 g lots and stored at 4 C

Sto k standard was prepared by first weighing out 1 000 g of triolein in a 100 ml beak r on an analytical balance and dissolv ing this in about 50 ml isopropanol Th solution was then transferred with 2 3 isopropanol rinses to a 100 ml volumetric fla k and diluted to 100 ml

Intermediat standards w re prepared by weighing out re spectively 3 75 7 5 15 0 and 22 5 g of the stock standard and diluting with i opropanol to a weight of 75 g The scale on the balance was accurate to the n arest 0 1 g so the last digit had t b stimated These standard were stored at room temperature in 100 ml brown screw cap bottles

Working standard w re prepared prior to every other run For e ch of these standards 0 5 ml of the interm diat stand rds previously de cribed were diluted with 9 ml of isopropanol and 0 5 ml of deionized wat r Th conc ntration of these standards rrespond d respectively to 50 100 200 and 300 mg% of t igly er de in serum

T tal chol t ol wa determined colorimetrically according t th pro edure d ribed in the T chnicon AutoAnalyz r M thod 1 gy N 24 (Appendix pag 146) Thi s miautomated method was orig lly d s ribed by Block Jarret and Levine [14] and was b sed on an earlier method of Levine and Zak (1964) [15] The basis of the method is the re ction of cholest rol with ferri hlorid n a ixture of con sulphuric acid and glacial acetic id t 90 C res lting in the formation of a coloured compound wri h n b re s red t 550 nm

TRIGLYCERIDES

To sampler II Wash receptable
Uppper level
Lower level
Tube size (inches)
o o45 Isopropanol
o o9o Acetylacetone reagent
o o73 Periodate in acetic acid
4b
Sample
Sampler II
o o81 Air
o o9o
o o9o Base reagent
o o9o
o 11o Waste from air removal "T"
Solvaflex tubing
•• Acidflex tubing
• Tygon tubing
Heating b
5o C
GO
Two double mixing coils
D1
KO
Single mixing coil
Time delay coil
Waste
Proportioning pump
Waste
Fl orometer
R corder
Prima y 405 mμ D AL Interference filter se ondary 3-71 Corning filter

Figure A III 2 health survey in the Reykjavik area Stage I 1967 - 68 - Men
AutoAnaly er flow diagram for the determination of serum triglycerides

Extraction (see page 14)

Reagents used for th cholesterol determination were as follows

Isopropanol (see page 14)

F rric chloride reagent This was prepared by weighing out on an analytical balance 1 375 g of ferric chloride ($FeCl_3$ $6H_2O$ MW 270 30 E Merck AG Darmstadt Germany) and dissolving this in 2 litre acetic acid (pro analysi (100%) E Merck AG Darmstadt Germany) followed by addition of 1 litre of sulphuric acid (pro analysi (95 97%) E Merck AG Darmstadt Germany) This reagent was stored in 1 litre brown screw cap bottles

Standards were prepared from pure cholesterol (cholesterin $C_{27}H_{46}O$; E Merck AG Darmstadt Germany)

A sto k standard was prepared by dissolving 500 mg of cholesterol in about 50 ml of isopropanol in a 100 ml b aker trans ferring the solution quantitatively with 2 3 isopropanol rinses to a 100 ml volumetric flask and making up to the mark with isopropanol Th stock standard was stored at room temperature in a brown 100 ml screw cap bottle

Working standard were prepared by diluting respectively 1 2 3 and 4 ml of stock standard to 100 ml with isopropanol The concentration of these standards corresponded to serum cholesterol concentrations of respectively 100 200 300 and 400 mg% Th y were stored at room temperature in brown 100 ml screw cap bottl s

Equipment A T chnicon AutoAnalyzer I was used This in lud d th following main components Sampler II fixed speed proportioning pups adjust bl h ating baths a colorimeter with a 15 mm tubular glass flow c ll a fluorimeter I and an 11 inch doubl pen recorder (Elliot Process Automation Ltd England)

AutoAn ly er runs for chole t rol and triglyceride determina t n w re c rried out every other working day

At the st rt of a run the cholest rol manifold was rinsed by first pumping through water for 5 minutes and then air for 3 inute Reag nts and isopropanol were then pumped through for

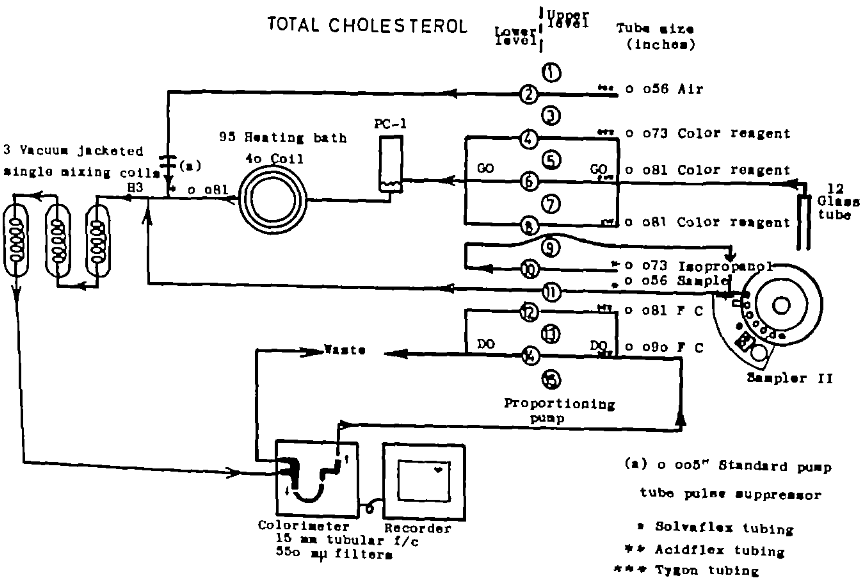


Figure A III 3 Health survey in the Reykjavik area Stage I 1967 - 68 - Autoanalyzer flow diagram for the determination of serum total cholesterol

Triglycerides and total cholesterol Quality control was maintained on the cholesterol and triglyceride determinations For this Control serum from Hyland Division Travenol Laboratories Inc California USA and Seronorm from Nyegaard & Co Oslo Norway were used Both were obtained from Bie & Berndsen Copenhagen Denmark in freeze dried form and imported by air They were transported in non insulated packages but supplies were placed in a refrigerator at 4 C immediately upon arrival at the clinic

From January 31st to May 27th 1968 Special Clinical Chemistry Control Serum was us d to monitor the triglyceride and total cholesterol determinations

From June 6th to July 4th Normal Clinical Chemistry Control Serum was used to monitor total cholesterol determinations

From July 9th to September 24th Seronorm was used to monitor total cholest rol determinations

Hyland serum was prepared for use by dissolving the contents f one ampoul in 5 ml of deionized water The solution was then transferred to about 8 1 5 ml cups and stored in a deep freeze abinet (20 to 18 C) For each lot of extractions one cup was usually thaw d and th control erum extracted at the same time as and in an identical fashion with the participants s rum samples During runs the participants serum extracts were interspersed with on and occasionally two or three control serum xtra ts

The Ny gaard s run was treated in a similar fashion

The re ult from the quality control program are hown in t bl s A III 3 4 Their chief statistical characteristics are ho n in tabl A III 5 p ge 24 Fig A III 4 on p ge 8 is a scatter di gram of th results obtained from Feb 1 t to May 27th

Of 25 alues for t iglycerid s in the Hyland peci l Control n 8 (32%) f ll o ts de the range (65 10 mg%) reported a ptable by the manuf cturers all of these ex eding the upper li t The me n val e was 62 9 mg% and the standard deviation wa 7 43 mg% with 2 d gre s of freedom The mean value is thus

8 minutes 1 through the cholesterol system and 3 through the triglyceride system *After this the baselines for cholesterol* and triglycerides were adjusted to 99%T and 8-12% respectively

Glass tubes of 2 ml capacity were used on the sampler tray These were placed in the plastic sample cup on the tray Because of their small size more sample had to be added during aspiration *Due to evaportion only four* samples were left on the tray at any one time Cholesterol and triglyceride standards in order of increasing concentration were included at the beginning and the end of each run Between every ten or so serum samples one of each series of standards (but never the highest one) were inserted The rate of sampling was 40 per hour and the sample to wash ratio was 2 1 The between-samples wash was isopropanol 1/

The cholesterol manifold (see fig 3) Tygon pump tubing was used except for Solvaflex tubing for the sample A twelve inch long Acidflex tube connected the outlet from the water bath to an H3 fitting The tube was replaced when it started to deform or about once every two months

The triglyceride manifold (see fig 2) Tygon pump tubing was used except for Acidflex tubing for the base reagent and Solvaflex tubing for the sample isopropanol and waste In between the heating bath and the colorimeter was a 40 foot delay coil 1 6 mm in internal diameter

The recorder chart reading was taken on the same or the next day and the results recorded on the appropriate station cards A standard curve was drawn on a transparent plastic card through the standard peaks with the aid of a plastic coated lead ruler and this curve was subsequently used to determine the concentration in the samples If peaks exceeded the highest standard peak on the card the corresponding samples were measured again after dilution from 1 1 to 1 4 as needed

Quality control

Beta-lipoproteins No quality control of the beta lipoprotein measurements was carried out

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1/ Before triglyceride determinations were started between sample washes were water otherwise isopropanol was used

Table A III 4

Health survey in th Reykjavik area Stage I 1967 - 68 Men
Values of total cholesterol in Hyland s Normal Clinical Chemistry
Control Serum and in Nyegaard s Seronorm

Date of extraction	Hyland: Total cholesterol values in mg% 1/	Nyegaard: Total cholesterol values in mg% 2/
6th June 1968	196	
11	189 192	
12	191	
19	188 190	
0	190	
21	190	
27	188	
28	184	
2nd July 1968	186	
4th	183	
9		90
10		94
12 Aug		94
15		100
16		81
23		96
27		100
28		93
2nd Sept		95
4th		86
5		100
11		93 95
13		97
17		98
20		99
24		96

1/ Ac ptabl values 195 10 rg%
2/ Re ommend d v lu 100 106mg%

Table A III 3

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Values of total cholesterol and triglycerides in Hyland s
Special Clinical Chemistry Control Serum

Date of extraction	Hyland	
	Total cholesterol values in mg% 1/	Triglycerides values in mg% 2/
31st Jan 1968		62
1 Feb	156	61 60
6th "	174	60
28 " "	174 176	
29 " "	166 160	70
14 Mar	174 174	75
18 "	166	60
19 "	167	59
20 "	162 170 165	62
21st "	158	59
22th "	162	60
29 " "	175	62
1st Apr	161	50
2nd		71
4th "	170	
8	166	69
17	172	72
18 "	172	
19	170	55
3d May	171 158	70 50
6 "	156	50
7 "	170	70
10	150	50
17 "	170	65
20	161	73
27	167	62

1/ Acceptable values 180 ± 10 mg%
2/ Acceptable values 55 ± 10 mg%

ignificantly greater than 55 mg% the difference being 7 9 mg% (This and subsequent values for standard deviations are based on only the first recorded value for each extract)

Of 30 valu s for total cholesterol in Hyland s Special Control Serum 16 (53%) fell outside the range (180- 10 mg%) reported as acceptable by the manufacturers all of these falling below the lower limit The mean value was 166 3 mg% and the standard deviation was 6 71 mg% with 23 degrees of freedom The mean values is thus significantly lower than 180 mg% the difference being 13 7 mg%

Of 12 values for total cholest rol in Hyland s Normal Control Serum one (184 mg%) fell just below the acceptable value (195 10 mg%) reported by the manufacturers The highest valu was 196 mg% The mean value was 189 6 mg% and the standard deviation was 3 41 mg% with 9 degrees of freedom The mean value is thus significantly lower than 195 mg% the differenc being 5 4 mg%

Of 17 values for total cholesterol in Nyegaard s Seronorm 14 (82%) fell outside the range (100 - 106 mg%) recommended by th manufacturers all of them falling short of the lower limit Th mean value was 94 3 mg% and the standard deviation was 5 7 mg% with 15 degrees of fre dom The mean valu is thus significantly lower than 103 mg% the difference being 8 7 mg% On the other hand 4 (24%) of the results fell outside the limits $103^{+}10$ mg%

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Stati tical comparison (Bartlett s te t) of the standard de iations in the total chol st rol determinations shows that th re i no significant difference (p 0 05) between the results obtained with th diff rent control era (χ^2(2) 4 98 compared with the 95% fra tile which is 5 99) The estimated common tandard de iation is 5 73 mg% with 47 d gree of freedom

From January 31st t May 27th 1968 both the triglyceride and th total hole t rol cont nt w re mea ured in all samples of Hyland s Spe ial Control Serum The correlation coeffi ient

Table A III 5

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Values of total cholesterol and triglycerides in control serum

		Total cholesterol	Triglycerides
Hyland s Special Clinical Chemistry Control Serum 31st Jan 1968 - 27th May 1968			
Number	n	24 1/	23 /
Mean	$\bar{x}$	166 3 mg%	62 9 mg%
Variance	s^2	45 07	55 17
s d	s	6 71	7 43
Min		150	50
Max		175	75
Range		25	25
Hyland s Normal Clinical Chemistry Control Serum 6th June 1968 - 4th July 1968			
Number	n	10 3/	
Mean	$\bar{x}$	189 5 mg%	
Variance	s^2	11 61	
s d	s	3 41	
Min		184	
Max		196	
Range		12	
Nyegaard s Seronorm 9th July 1968 - 24th Sept 1968			
Number	n	16 4/	
Mean	$\bar{x}$	94 3 mg%	
Variance	s^2	26 76	
s d	s	5 17	
Min		81	
Max		100	
Range		19	

1/ Acceptable values 180 ± 10 mg% 2/ 56 ± 10 mg% 3/ 195 ± 10 mg%
4/ Recommended value 100 106mg%

significantly greater than 5 mg% the difference being 7 9 mg% (This and subsequent values for standard deviations are based on only the first recorded value for each extract)

Of 30 values for total cholesterol in Hyland s Special Control Serum 16 (53%) fell outside the range (180$^+$ 10 mg%) reported as acceptable by the manufacturers all of these falling below the lower limit The mean value was 166 3 mg% and the standard deviation was 6 71 mg% with 23 degrees of freedom The mean values is thus significantly lower than 180 mg% the difference being 13 7 mg%

Of 12 values for total cholesterol in Hyland s Normal Control Serum one (184 mg%) fell just below the acceptable value (195-10 mg%) reported by th manufacturers The high st value was 196 mg% The mean value was 189 6 mg% and the standard deviation was 3 41 mg% with 9 degrees of freedom The mean value is thus significantly lower than 195 mg% the difference being 5 5 mg%

Of 17 values for total cholesterol in Nyegaard s Seronorm 14 (82%) fell outside the range (100 106 mg%) recommended by the manufacturers all of them falling short of the lower limit The mean value was 94 3 mg% and the standard deviation was 5 7 mg% with 16 degrees of freedom The mean value is thus significantly lower than 103 mg% th difference being 8 7 mg% On the other h nd 4 (24%) of the results fell outside the limits 103 10 mg%

- -

tati tical comparison (Bartlett s test) of the standard de i tions in the t tal cholesterol determinations show that th re is no ignificant difference (p 0 05) between the results obtained with th different control sera (χ^2( ) 4 96 compared w th th 95% fractile which is 5 99) The estimated common tandard de i tion i 5 73 mg% with 47 d gre s of freedom

From Janu ry 31st to May 27th 1968 both the triglycerid and th t tal chol terol cont nt were measured in all samples of Hyland s pe ial Control Serum The correlation coefficient

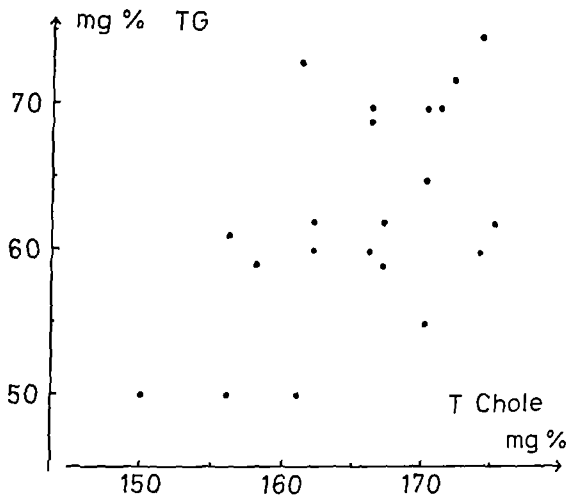


Figure A III 4 Scatter diagram showing values of total cholesterol and triglycerides in Hyland s Special Clinical Chemistry Control Serum Correlation coefficient 0 554

was 0 554 and the correlation therefore significant (p 0 01 Fishers test) [1/]

Handling of data

All the results of the first visit were recorded on special forms termed station cards The data were punched on cards as they became available for use in the computerized printout of medical reports and for data analysis Punching was handled by IBM in Iceland but the printout of medical reports by the University Computer Centre (IBM 1620) and by IBM in Iceland (IBM 1401)

Before the parti ipant returned for his second visit his medical report was available and had be n checked by two physi clans During the medical examination a physician again checked through th participant medical record and compared it with the station card and other basic documents as required

All the data obtained in tage I of the mal survey are stored on magn ic tape Data analysis with respect to this re port was carried out at th Icelandic Computer Centre (IBM 360)

Before any analysis of data was started all th results were checked by the comp ter and any valu s which fell outside c rtain l mits were printed out and compared with the original data f r revis on Th limit were as follows

Beta lipoprot ins	0 6 and	4 5 mm IC	
Triglycerides	12	310	mg%
Tot l chole terol	140	- 500	

1 e s rer nts on Hyl nd serum were not begun until ua y lt sh ld be ention d that the standard deviation f 14 ren nt or pooled serum from Dec mber 8th 1967 t J uary 19th 1968 was 7 87 mg% see also the Appendix abl A III 50

Table A III 6 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values in men Total response 75 1%[1/]

Values in mm Immunocrit	Age in years																All age-groups
Class width 0 2 mm	34	37	40	42	44	45	47	48	49	50	51	52	54	56	58	61	
- 9	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	3
1 0 - 1 1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1 2 - 1 3	0	0	0	0	2	0	1	0	0	0	0	0	0	0	1	1	5
1 4 - 1 5	1	2	1	0	0	3	2	3	1	0	0	2	1	1	0	0	17
1 6 - 1 7	1	3	5	3	3	2	5	1	4	1	2	0	4	1	2	0	37
1 8 - 1 9	8	4	8	7	9	3	6	4	4	5	5	5	4	4	1	4	81
2 0 - 2 1	6	3	4	13	10	6	13	13	4	7	5	10	9	9	3	6	121
2 2 - 2 3	4	8	11	9	10	12	3	6	3	3	3	1	1	6	2	7	89
2 4 - 2 5	3	7	6	6	4	5	3	3	2	4	6	3	8	3	1	1	65
2 6 - 2 7	2	1	3	1	3	4	2	2	1	0	1	0	2	2	1	0	25
2 8 - 2 9	4	1	4	4	3	1	2	6	3	2	1	5	2	0	3	0	41
3 0 - 3 1	1	3	2	0	5	3	2	9	0	3	4	1	1	0	0	0	34
3 2 - 3 3	1	1	2	2	1	0	3	1	0	1	0	0	0	1	0	0	13
3 4 - 3 5	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	4
3 6 - 3 7	0	1	1	1	0	0	0	0	0	0	1	0	1	0	0	0	5
3 8 - 3 9	0	1	0	0	0	0	1	2	0	0	0	0	0	0	2	0	6
4 0 - 4 1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	2
4 2 - 4 3	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
4 4 - 4 5	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	2
4 6	0	0	0	0	0	1	1	0	0	1	0	0	0	0	0	0	3
Tot 1 (N)	33	38	48	47	51	40	46	52	23	27	29	27	33	27	16	19	556
N as % of no investigated	23 4	25 5	30 0	28 7	30 5	26 7	26 6	29 7	18 1	23 1	23 2	21 3	26 0	21 1	18 6	21 8	25 2

1/ % inve tigated ... stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 ... B ca ... e of the appointment system the 556 men can be considered as a stratified random ... April ... t th s investigated

RESULTS

In presentation of the results by tables and graphs the age groups have generally been collected in 5-year cohorts according to the accepted practice thus 30 - 34 years 35 - 39 years etc[1/] Due to the way the age groups were selected the numbers of age groups in ach cohort differ Thus there is only one age group in the 30 - 34 cohort namely 34 year old men whereas in the 45 49 cohort th re are four age groups Reading of tables and graphs is thereby made easi r but at the same time simplefied It should be noted that the number of values varies from one cohort to the next this being smallest in the youngest and the old st cohorts There are altogether 7 cohorts covering the age span from 30 to 64 y ars

Physiological measurements rarely follow strictly a normal distribution but results from such measurements are however frequently normally distributed to an acc ptable apprpximation Wh re this is not the case their respective logarithms frequent ly re and the distribution is then said to b lognormal In th pre ent tudy it has been investig ted whether th results conform more closely to a normal or a lognormal distribution

In the prep ration of tables and graphs there has been much st ndardiz tion partly in order that a comput r could be used effi iently

A computer was us d to prep re and print out the results in the following tables and graphs

) Frequ ncy tables both single (Tables A III 6 9 and 12 age gr ps not llected in c hort) and double (Tables A III 15 35 ag gro ps olle t d in cohort) In thes tables th results were gr uped Th tabl s are in a w y basic to most oth r tabl s and graphs in this report

b) T bl f distribution functi ns (Tables A I I 7 10 and 13) The t bl s how what percentag of the results from each age gro p qual to or lower than (s) c rt in stated valu s

1/ I few s s individual age group tabl s were prepared th s are presented in the Appendix u h t bles are not disc d in th main t xt but are o casionally referred to in footnot s

Table A III 6 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values in men Total response 75 1%[1/]

Values in mm Immunocrit	Age in years																All age-groups
Class width 0 2 mm	34	37	40	42	44	45	47	48	49	50	51	52	54	56	58	61	
- 9	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	3
1 0 - 1 1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1 2 - 1 3	0	0	0	0	2	0	1	0	0	0	0	0	0	0	1	1	5
1 4 - 1 5	1	2	1	0	0	3	2	3	1	0	0	2	1	1	0	0	17
1 6 - 1 7	1	3	5	3	3	2	5	1	4	1	2	0	4	1	2	0	37
1 8 - 1 9	9	4	8	7	9	3	6	4	4	5	5	5	4	4	1	4	81
2 0 - 2 1	6	3	4	13	10	6	13	13	4	7	5	10	9	9	3	6	121
2 2 - 2 3	4	8	11	9	10	12	3	6	3	3	3	1	1	6	2	7	89
2 4 - 2 5	3	7	6	6	4	5	3	3	2	4	6	3	8	3	1	1	65
2 6 - 2 7	2	1	3	1	3	4	2	2	1	0	1	0	2	2	1	0	25
2 8 - 2 9	4	1	4	4	3	1	2	6	3	2	1	5	2	0	3	0	41
3 0 - 3 1	1	3	2	0	5	3	2	9	0	3	4	1	1	0	0	0	34
3 2 - 3 3	1	1	2	2	1	0	3	1	0	1	0	0	0	1	0	0	13
3 4 - 3 5	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	4
3 6 - 3 7	0	1	1	1	0	0	0	0	0	0	1	0	1	0	0	0	5
3 8 - 3 9	0	1	0	0	0	0	1	2	0	0	0	0	0	0	2	0	6
4 0 - 4 1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	2
4 2 - 4 3	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
4 4 - 4 5	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	2
4 6	0	0	0	0	0	1	1	0	0	1	0	0	0	0	0	0	3
Total (N)	33	38	48	47	51	40	46	52	23	27	29	27	33	27	16	19	556
N as % of no investigated	23 4	25 5	30 0	28 7	30 5	26 7	26 6	29 7	18 1	23 1	23 2	21 3	26 0	21 1	18 6	21 8	25 2

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 B iuse f the appointment system the 556 men can be considered as a stratified random sample cf thos investigated

Table A III 8

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Numeri al characteristi s of the distributions of serum B-lipoprotein values in men Total respons 75 1%[1/]

B-lipoprotein values in mm Immunocrit	Age in years						
	34	37	40 42 44	46,47 48,49	50 51 52 54	56 58	61
Mean (x̄)	2 22	2 39	2 29	2 32	2 30	2 24	2 34
Variance	28	47	30	42	31	27	05
s d (s)	53	68	55	64	55	52	26
s/x̄	24	28	24	28	24	23	13
5% centile[2/]	1 48	1 44	1 63	1 46	1 63	1 56	1 34
10%	1 76	1 60	1 76	1 62	1 77	1 70	1 80
20%	1 84	1 83	1 88	1 85	1 89	1 89	1 87
30%	1 92	2 04	1 99	1 99	1 99	2 00	1 97
40%	2 02	2 21	2 10	2 08	2 06	2 07	2 04
50%	2 13	2 30	2 20	2 18	2 14	2 14	2 10
60%	2 29	2 40	2 30	2 31	2 37	2 25	2 16
70%	2 49	2 51	2 44	2 53	2 48	2 36	2 22
80%	2 77	2 98	2 72	2 85	2 77	2 58	2 27
90%	2 94	3 39	3 02	3 09	3 00	2 86	2 32
95%	3 22	3 77	3 26	3 35	3 13	3 32	2 36
Min	90	1 10	1 20	80	1 40	1 30	1 30
Max	3 40	4 20	4 50	5.00	5 50	3 80	2 40
Rang	2 50	3 10	3 30	4 20	4 10	2 50	1 10
of ure (N)	33	38	146	161	116	43	19
% of no st g t d	23 4	25 5	29 7	25 8	23 4	20 1	21 8

1/ % n est t d t g I st rted in Nov 1967 b t the β lipo prot i re sure nts b gan in May 1968 Because of th appoint t a ate t 556 e an be considered as a stratified random e of thos in estig ted

Cutt ng point b lo whi h are f und 5 10 20 etc per cent of h l

Table A III 7

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Cumulative distributions of serum B-lipoprotein values in men
Total response 75 1%[1/]

B-lipoprotein values in mm Immunocrit	Age in years						
	34	37	40 42 44	46 47 48 49	50 51 52 54	56 58	61
≤ 9	3 0	0	0	1 2	0	0	0
- 11	3 0	2 6	0	1 2	0	0	0
- 13	3 0	2 6	1 4	1 9	0	2 3	5 3
- 15	6 1	7 9	2 1	7 5	2 6	4 6	5 3
- 17	9 1	15 8	9 6	14 9	8 6	11 6	5 3
- 19	33 3	26 3	26 0	25 5	25 0	23 3	26 3
- 21	51 5	34 2	44 5	47 8	51 7	51 2	57 9
- 23	63 6	55 3	65 1	62 7	58 6	69 8	94 7
- 25	72 7	73 7	76 0	70 8	76 7	79 1	100 0
- 27	78 8	76 3	80 8	76 4	79 3	86 0	100 0
- 29	90 9	78 9	88 4	83 8	87 9	93 0	100 0
- 31	93 9	86 8	93 1	92 5	95 7	93 0	100 0
- 33	97 0	89 5	96 6	95 0	96 5	95 3	100 0
- 35	100 0	92 1	96 6	95 6	97 4	95 3	100 0
- 37	100 0	94 7	97 9	95 6	99 1	95 3	100 0
- 39	100 0	97 4	97 9	97 5	99 1	100 0	100 0
- 41	100 0	97 4	97 9	98 8	99 1	100 0	100 0
- 43	100 0	100 0	98 6	98 8	99 1	100 0	100 0
- 45	100 0	100 0	100 0	98 8	99 1	100 0	100 0
No of measurem (N)	33	38	146	161	116	43	19
N as % of no investigated	23 4	25 5	29 7	25 8	23 4	20 1	21 8

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 556 men can be considered as a stratified random sample of those investigated

Tabl A III 8

Health survey in the Reykjavik area Stage I 1967 - 68 Men
Numerical characteristics of the distributions of serum B-lipo prot in values in men Total response 75 1%[1/]

B-lipoprotein values in mm Immunocrit	Age in years						
	34	37	40 42 44	46 47 48,49	50 51 52 54	56 58	61
Mean (x̄)	2 22	2 39	2 29	2 32	2 30	2 24	2.34
Variance	28	47	30	42	31	27	05
s d (s)	53	68	55	64	55	52	26
s/x̄	24	28	24	28	24	23	13
5% centile[2/]	1 48	1 44	1 63	1 46	1 63	1 56	1 34
10%	1 76	1 60	1 76	1 62	1 77	1 70	1 80
20%	1 84	1 83	1 88	1 85	1 89	1 89	1 89
30%	1 92	2 04	1 99	1 99	1 99	2 00	1 97
40%	2 02	2 21	2 10	2.38	2 06	2 07	2 04
50%	2 13	2 30	2 20	2 18	2 14	2 14	2 10
60%	2 29	2 40	2 30	2 31	2 37	2 25	2 16
70%	2 49	2 51	2 44	2 53	2 48	2 36	2 22
80%	2 77	2 98	2 72	2 85	2 77	2 58	2 27
90%	2 94	3 39	3 02	3.09	3 00	2 86	2 32
95%	3 22	3 77	3 26	3.35	3 13	3 32	2 34
Min	90	1 10	1 20	80	1 40	1 30	1 30
Ma	3 40	4 20	4 50	5.00	5 50	3 80	2 40
Rang	2 50	3 10	3 30	4 20	4 10	2 50	1 10
No of me s rem (N)	33	38	146	161	116	43	19
N a % of no n tig t d	23 4	25 5	29 7	25 8	23 4	20 1	21 8

1/ % in at gated Stag I tarted in Nov 1967 b t the β lipo prote n mea urements began in May 1968 Becaus of the appoint ment yst n the 68 en can be con id red as a tratified random sarple of thos inv stigated

2 Cutting point b low which are found 5 10 20 etc per c nt of h l

Table A III 7

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Cumulative distributions of *serum* B-lipoprotein values in men
Total response 75 1%[1/]

B-lipoprotein values in mm Immunocrit	Age in years 34	37	40 42 44	46 47 48 49	50 51 52 54	56 58	61
≤ 9	3 0	0	0	1 2	0	0	0
- 1 1	3 0	2 6	0	1 2	0	0	0
- 1 3	3 0	2 6	1 4	1 9	0	2 3	5 3
- 1 5	6 1	7 9	2 1	7 5	2 6	4 6	5 3
- 1 7	9 1	15 8	9 6	14 9	8 6	11 6	5 3
- 1 9	33 3	26 3	26 0	25 5	25 0	23 3	26 3
- 2 1	51 5	34 2	44 5	47 8	51 7	51 2	57 9
- 2 3	63 6	55 3	65 1	62 7	58 6	69 8	94 7
- 2 5	72 7	73 7	76 0	70 8	76 7	79 1	100 0
- 2 7	78 8	76 3	80 8	76 4	79 3	86 0	100 0
- 2 9	90 9	78 9	88 4	83 8	87 9	93 0	100 0
- 3 1	93 9	86 8	93 1	92 5	95 7	93 0	100 0
- 3 3	97 0	89 5	96 6	95 0	96 5	95 3	100 0
- 3 5	100 0	92 1	96 6	95 6	97 4	95 3	100 0
- 3 7	100 0	94 7	97 9	95 6	99 1	95 3	100 0
- 3 9	100 0	97 4	97 9	97 5	99 1	100 0	100 0
- 4 1	100 0	97 4	97 9	98 8	99 1	100 0	100 0
- 4 3	100 0	100 0	98 6	98 8	99 1	100 0	100 0
- 4 5	100 0	100 0	100 0	98 8	99 1	100 0	100 0
No of measurem (N)	33	38	146	161	116	43	19
N as % of no investigated	23 4	26 6	29 7	25 8	23 4	20 1	21 8

1/ % investigated Stage I started in *Nov 1967 but the β* lipoprotein measurements began in May 1968 Because of the appointment system the 556 men can *be considered as a stratifi* ed random sample of those investigated

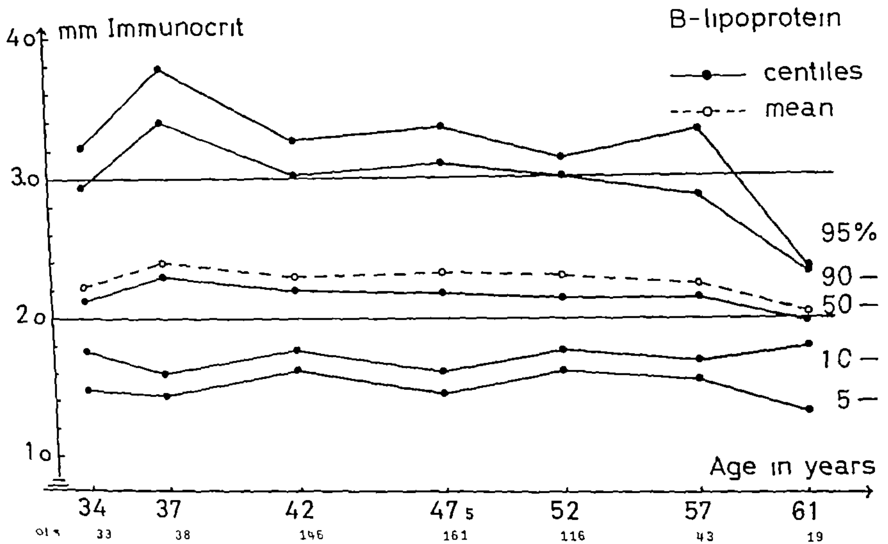


Figure A III 5 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Diagram showing the mean median and a few centiles of the distributions of β-lipoprotein values in 7 cohorts (34 yr) (37 yr) (40 42 44yrs) (46 47 48 49 yrs) (50 51 52 54 yrs)

The stated values are the right hand side end points of the class es in the frequ ncy tables

c) T bles of chi f statistical characteristics of the results in each cohort Mean varianc standard deviation coefficient of variation 5 10 20 30 40 50 60 70 80 90 95% centiles minimum and maximum valu and the rang (Tables A III 6 11 and 14)

d) Hi tograms of the results from each cohort (Figs A III 6 11 and 15) For preparation of histograms the computer grouped the result into 17 intervals and printed out the symbol × for each percentage falling within each interval The height of the column is therefore accurate to within ± 0 5% The end columns represent results falling outside certain limits these being the are for all 7 cohorts Columns in thes end intervals are eparat d from other columns by the symbol —/—[1/] The histograms indicate th po ition and the shape of the d nsity functions of th distribution functions of the result and how they change w th ag

) Fr ctile diagrams (Fig A III 7 12 and 16) of the distribu tion fun tions for the cohorts 30 34 40 44 50 59 and 60 64 years In a oordinate y tem the ordinate s ale i transformed i uch way that the graph of a normal distribution function straight lin In thos fractile diagrams presented here the graph are not drawn but a few points from the graph of the (cumul tive) distribution function of the results are plotted n th coordinate yst m These point should lie near a str ght line if the results re n rmally distributed The point s le t d correspond to the right hand side end points of th l on the baselin of the aforemention d histograms xc pt for th points wh re th values of the distrib tion func t n l ≤ 005 r ≥ 995 imilar fractile diagrams w re also p pared for th logarithm of the result (Figs A III 8 13 and 17) [1/]

In addition to the ab ve mentioned tabl s and figure this repo t cont ins three type of graphs

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1/ See a ore deta l d de ription in th Appendix

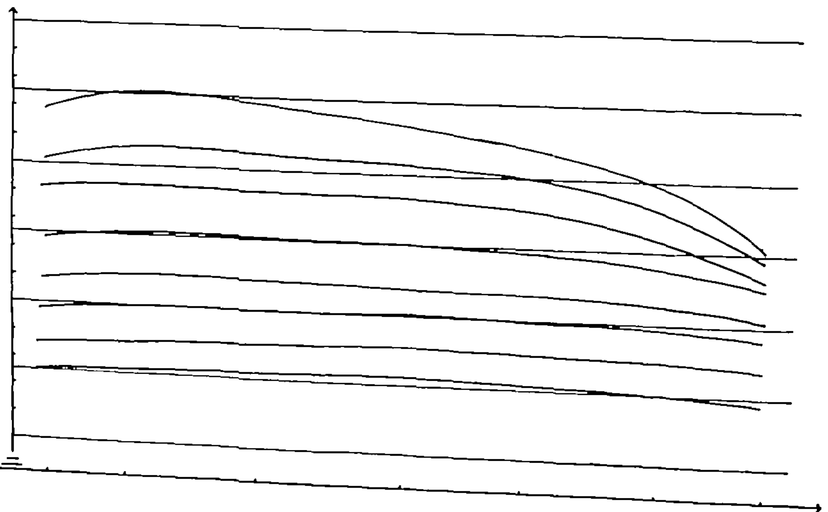


Figure A III 5b Lye fitted curves (Obs! highly subjectivo)5 10 30 50 70 80 90 95% centiles

% 30 20 10

No 116
Age 50 51
52 54 yrs

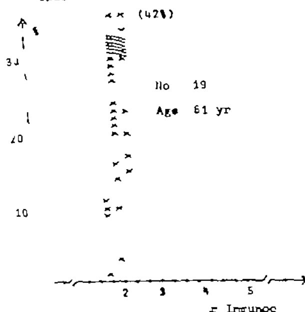
2 3 4 5

Class width 0 3 mm Immunoc

No #3
Age 56 58 yrs

2 3 4 5

mm Immunoc



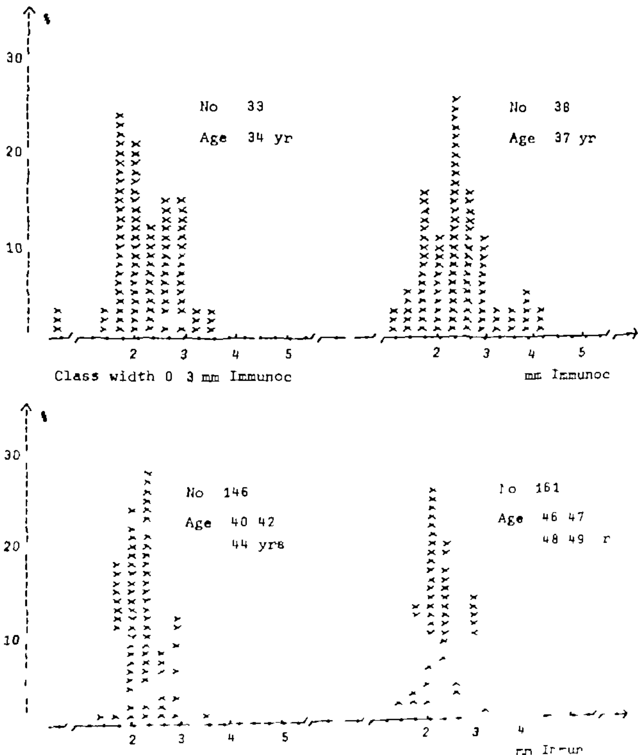
1/ % i e tigated Stag I t rted in Nov 1967 but the β lipo prot in mea rements began in May 1968 Because of th appo ntment y tem th 566 r n can b considerd as a strati fied random arpl of those inve tig ted

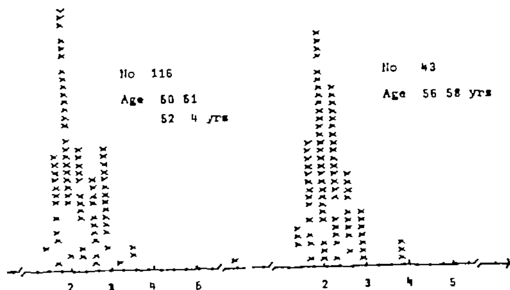
Figure A III 6

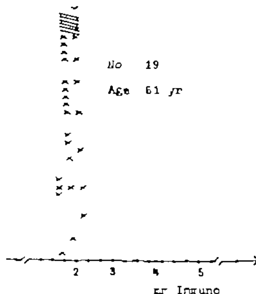
Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Histograms showing distributions of serum β-lipoprotein values in men

Total response 75 1 %[1/]

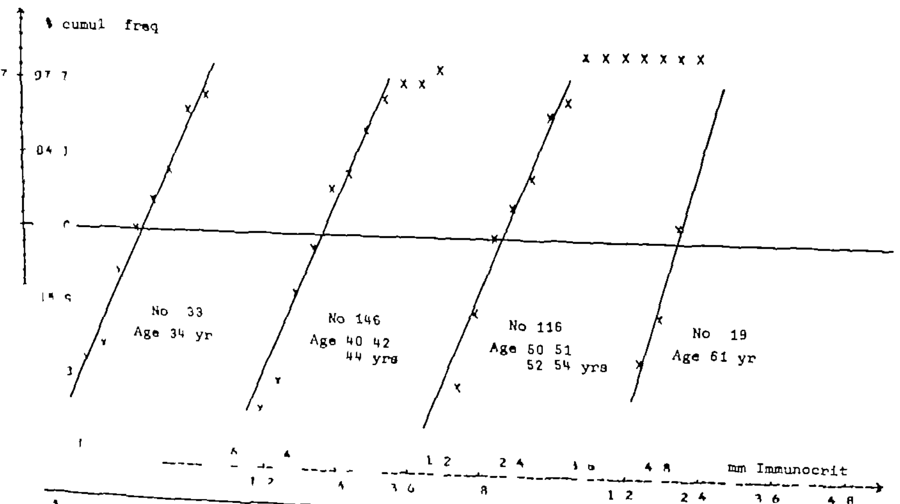






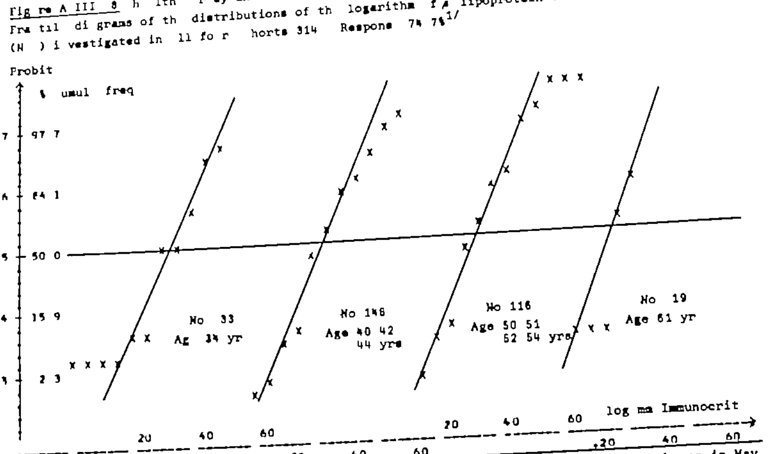
/ % in stig ted t g I start d in No 1967 b t th lipo prot in meas rem t beg n i May 1968 Be ause of the ppoint nt y t the 656 n be consid rd a tr ti fi a na m arpl f thos in t g t d

Figure A III 7 Health survey in the Reykjavik area Stage I 1967- 68 -Men
Fractile diagrams of the distributions of serum B-lipoprotein values in men Total number (No) 314 investigated in all four cohorts Response 4 7% 1/



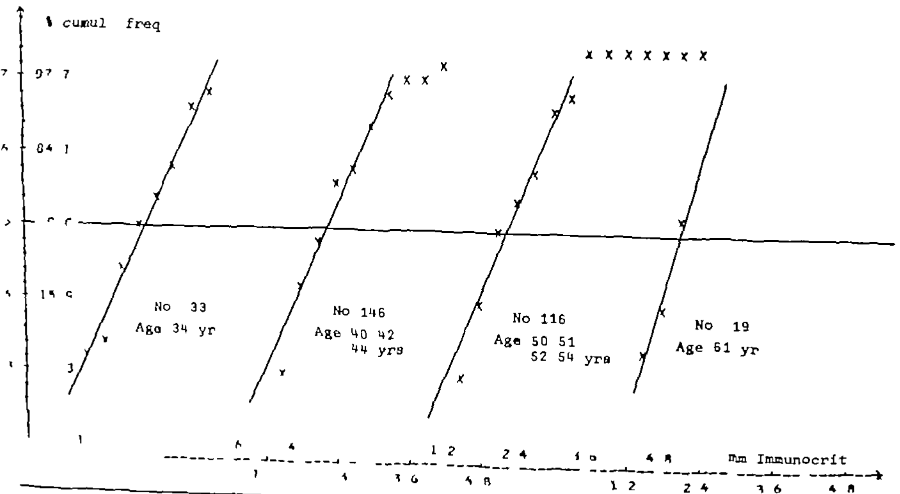
% investigated tage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 because of the appointment system the 314 men can be considerd as a stratified random sampl of those investigated

Fig re A III 8 h lth r ey in th Reykjavik area Stage I 1967 68 Men Total number
Fra til di grams of th distributions of th logarithm f β lipoprotein valu s in men
(N) i vestigated in ll fo r horts 314 Respons 74 7%[1]



1/ % investigated Stage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Because of th appointment system the 314 men can be considerd as a stratified random sample of those investigated

Figure A III 7 Health survey in the Reykjavik area Stage I 1967- 68 -Men
Fractile diagrams of the distributions of serum B-lipoprotein values in men Total number (No) 314 investigated in all four cohorts Response 74 7% 1/



1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 314 men can be considerd as a stratified random sample of those investigated

f) Graphs showing th variation of the means and a few main fractiles with age (Figs A III 5 10 and 18) These were pre pared by plotting on graph paper the values for each cohort according to the tables of chief statistical characteristics (see paragraph c)

g) Graphs showing the weekly means both standardized and not standardized togeth r with the weekly standard deviations dur ing the period from December 1967 to the beginning of July 1968 (Figs A III 9 14 and 19)

h) Graphs showing how the correlation coefficients vary with age (Fig A III 20) They are based on tables A III 15 - 35

Beta lipoproteins

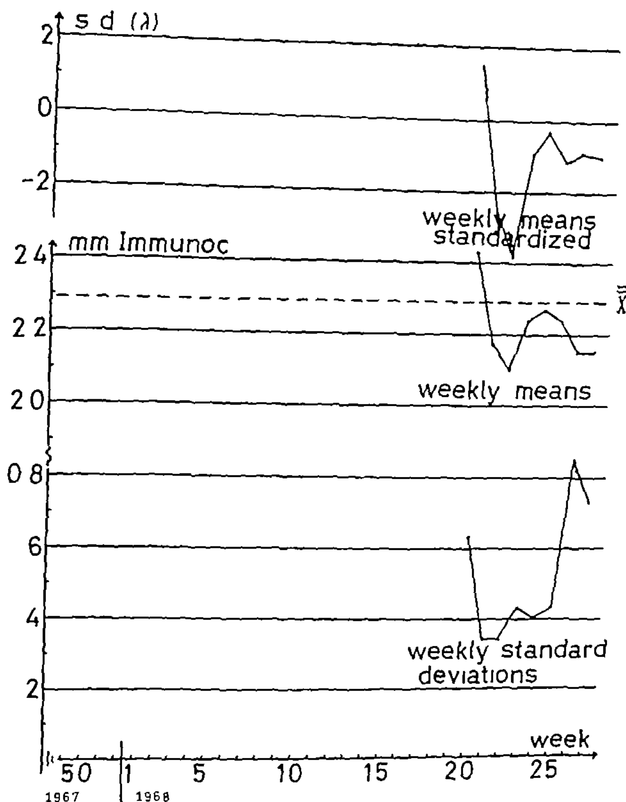
Analys s were started by the middle of May Beta lipoproteins were measured in sera from 556 participants and these turned out to be between 20% and 30% of each cohort (Table A III 8 page 31) The results are presented as mm Immunocrit (abbreviated mm IC) to an accuracy of 0 1 mm

From fractile diagrams and the histograms (Figs A III 6 7) th results from each cohort appear to be approximately normally distributed There are however some deviations as seen clear ly in fig A III 5 and as suggested by the histograms The distributions are slightly skew with a slightly longer tail towards th right except in the old st age group This is shown g by the fact that mean values are about 0 1 mm IC higher than the median valu 1/

Th coefficient of variation vary betwe n 0 23 and 0 28 x pt in the oldest cohort where it is 0 13 Th log rithm of the results is therefore also approximat ly normally distri but d as shown by the fractile diagrams (Fig A III 8) In fact the approximation appears to be closer to a lognormal distribution than to a normal distribution

Means 50% fra tiles (medians) and lower fractiles appear to rea nable approximation to b age independ nt Thus the me ns 50% 10% and 5% fractile are about 2 3 2 2 1 7 and

1/ See also b_2 (oeffici nt of excess) in Table A III 45 in App ndix



Obs per week 26-65

Figure A III 9 Health survey in the Reykjavik area Stage I 1967 '68 - Men Weekly mean values ($\bar{x}$) weekly standard deviations (s) and weely mean values standardized ($\lambda = (\bar{x} - \bar{\bar{x}})\sqrt{n}/s$) of serum β- lipo protein values in men n = obs pr week --- $\bar{\bar{x}}$ grand mean

1 6 mm IC respectively

The high r fractiles seem to be to a reasonable approximation age independent up to the age of 50 but to decrease considerably over the next decade this decrease being about 0 6 mm IC for the 90% and 95% fractiles (Fig A III 5 p 32) Thus the 90% and 95% fractiles are about 3 0 mm IC and 3 3 mm IC for the age interval 35 50 years

Fig A III 9 p 38 shows graphs of the means ($\bar{x}$) and standard deviations (s) for each week in the period from th start of th survey in the beginning of December 1967 up to the summer vacation in the beginning of July 1968 where th number of we kly measurements was great r than 9 There is also a gr ph of th standardized weekly deviations (λ) from the grand mean ($\bar{\bar{x}}$) These deviations are computer calculated according to the formula λ ($\bar{x}$ $\bar{\bar{x}}$) $\sqrt{n}$ /s where s is the weekly standard deviation and n is the number of results per week As previous ly mentioned and as s en on th diagram beta lipoprotein deter minations were not started until the middle of May 1968 376 results or some 68% of the total number of results is from the period up to the summer vacation (See a further note in the discus ion)

Total chole t rol

Analyses were carried out from the beginning of th survey and continued throughout the period of the survey Total chol est rol wa measured in 2194 participants or 99 6% of thos who attended the clinic Th re re no results for 19 participants the rea on being that a blood sample could not be collected in th tim a ailable or these samples were lost by accidental pillage Th results are presented as mg% (mg/100 ml) to an a uracy of 1 mg%

From the fractil diagrams and th histograms the results ppear t be normally distributed (Figs A III 11 12) There are howe er light de iation as seen clearly in fig A III 10 and s gg sted by the hi t grams for the young r cohorts The distribution are lightly sk w with a somewhat longer tail to th ght This is shown i a by the fact that mean values re bout 2 4 mg% high r than th medi n values

Table A III 9 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum total cholesterol values in men Total response 75 1%[1/]

Values in mg/100 ml (mg%)	Age in years																All age-groups
Class width 10 mg%	34	37	40	42	44	46	47	48	49	50	51	52	54	56	58	61	
≤ 160	2	1	0	2	0	1	0	0	0	0	2	3	0	1	1	0	13
161 - 170	2	0	0	3	1	0	2	3	0	0	1	1	0	1	1	1	16
171 - 180	3	5	3	5	2	2	2	3	1	2	1	2	0	1	1	3	36
181 - 190	7	8	6	4	6	4	2	3	2	8	2	5	4	3	5	3	72
191 - 200	15	7	8	11	11	3	7	5	6	2	3	4	5	4	1	3	95
201 - 210	6	8	9	2	8	8	17	5	6	3	3	8	7	12	2	3	107
211 - 220	10	12	15	10	15	7	19	13	7	8	7	7	10	7	2	5	154
221 - 230	10	12	15	19	20	11	13	13	11	4	9	11	11	9	9	6	183
231 - 240	18	19	17	16	10	11	16	22	8	8	14	9	8	5	7	14	202
241 - 250	14	7	14	18	16	11	16	20	16	14	9	12	7	12	12	9	207
251 - 260	14	22	19	9	16	23	10	15	10	14	17	16	19	20	6	6	236
261 - 270	6	13	12	14	13	9	15	12	11	11	13	12	7	10	10	3	171
271 - 280	11	7	10	10	15	10	13	16	15	7	11	8	14	11	5	4	167
281 - 290	7	10	8	9	10	14	12	14	15	12	6	5	5	9	5	10	151
291 - 300	3	7	10	8	8	5	8	9	5	8	12	7	9	2	7	3	111
301 - 310	2	3	3	7	3	6	4	9	4	4	3	5	7	7	0	4	71
311 - 320	4	3	4	3	2	11	5	3	3	1	2	5	4	3	1	4	58
321 - 330	2	2	1	7	4	0	3	2	2	2	1	5	4	2	3	1	41
331 - 340	1	0	2	1	1	2	2	4	2	2	7	1	2	2	4	1	34
341 - 350	2	0	1	1	3	5	2	1	0	3	0	0	3	1	1	1	24
351 - 360	1	0	0	2	0	0	0	1	0	0	1	0	0	1	2	1	9
361 - 370	0	1	2	0	0	2	0	0	0	1	0	0	0	1	0	1	8
371 - 380	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	4
381 - 390	0	1	0	1	0	2	0	0	0	1	0	0	0	1	0	0	6
391 - 400	0	0	1	0	0	1	2	0	2	0	0	0	0	0	0	0	6
401 ≤	0	1	0	1	1	1	2	2	1	1	1	0	0	1	0	0	12
Total (N)	141	149	160	163	165	149	172	175	127	117	125	126	127	126	85	87	2194
N as % of no investigated	100	100	100	99 4	98 7	99 3	99 4	100	100	100	100	99 2	100	98 4	98 8	100	99 6

1/ % investigated

Tabl A III, 11

Health survey in the Reykjavik area Stage I 1967 68 - Men
Numerical characteristics of the distributions of serum total cholesterol values in men Total response 75 1%[1]

Total chole values in mg/100ml	Age in years						
	34	37	40 42 44	46 47 48 49	50 51 52 54	56 58	61
Mean ($\bar{x}$)	241 99	246 19	249 86	257 74	257 01	256 28	255 18
Variance	1866 13	1713 40	1835 16	2034 89	1828 26	1934 08	2058 52
s d (s)	43 19	41 39	42 83	45 10	42 75	43 97	45 37
$s/\bar{x}$	18	17	17	17	17	17	18
5 % centile	180 57	182 31	185 75	193 43	187 21	186 19	181 67
10 %	190 57	191 79	196 10	205 03	202 64	202 00	196 17
20 %	199 97	211 17	214 69	219 76	220 79	220 61	219 30
30 %	217 80	223 58	225 20	232 41	234 47	233 25	232 00
40 %	231 28	233 97	235 20	243 07	246 69	245 67	238 21
50 %	239 11	244 07	245 92	253 17	255 58	254 15	246 61
60 %	248 79	255 23	256 59	264 71	264 45	262 80	259 17
70 %	258 86	263 04	268 60	277 00	276 38	274 06	281 40
80 %	275 77	277 93	282 87	288 39	291 89	288 21	290 10
90 %	296 83	294 93	302 19	310 82	310 24	315 25	313 75
95 %	320 38	312 33	324 33	333 35	330 71	336 25	337 80
Min	144 00	156 00	158 00	158 00	136 00	156 00	168 00
Max	378 00	416 00	460 00	512 00	420 00	401 00	380 00
Range	234 00	260 00	302 00	354 00	284 00	245 00	212 00
No of me urem (N)	141	149	488	623	495	211	87
N as % of no. inv stigat d	100 0	100 0	99 4	99 7	99 8	98 6	100 0

1/ % inv stigated

2/ Cutti g points below which are found 5 10 20 etc per cent of the values

Table A III 10

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Cumulative distributions of serum total cholesterol values in men
Total response 75 1%[1/]

Total cholesterol values in mg/100ml (mg%)	Age in years						
	34	37	40,42 44	46,47 48 49	50,51 52 54	56,58	61
≤ 160	1 4	7	4	2	1 0	9	0
- 170	2 8	7	1 2	1 0	1 4	1 9	1 1
- 180	5 0	4 0	3 3	2 2	2 4	2 8	4 6
- 190	9 9	9 4	6 6	4 0	6 3	6 6	8 0
- 200	20 6	14 1	12 7	7 4	9 1	9 0	11 5
- 210	24 8	19 5	16 6	13 2	13 3	15 6	14 9
- 220	31 9	27 5	24 8	20 5	19 8	19 9	20 7
- 230	39 0	35 6	35 9	28 2	26 9	28 4	27 6
- 240	51 8	48 3	44 7	37 4	34 7	34 1	43 7
- 250	61 7	53 0	54 5	47 5	43 2	45 5	54 0
- 260	71 6	67 8	63 5	56 8	56 6	57 8	60 9
- 270	75 9	76 5	71 5	64 4	65 2	67 3	64 4
- 280	83 7	81 2	78 7	73 0	73 3	74 9	69 0
- 290	88 6	87 9	84 2	81 9	79 0	81 5	80 5
- 300	90 8	92 6	89 5	86 2	86 3	85 8	83 9
- 310	92 2	94 6	92 2	89 9	90 1	89 1	88 5
- 320	95 0	96 6	94 1	93 4	92 5	91 0	93 1
- 330	96 5	98 0	96 5	94 5	94 9	93 4	94 2
- 340	97 2	98 0	97 3	96 1	97 4	96 2	95 4
- 350	98 6	98 0	98 4	97 4	98 6	97 2	96 5
- 360	99 3	98 0	98 8	97 6	98 8	98 6	97 7
- 370	99 3	98 7	99 2	97 9	99 0	99 0	98 8
- 380	100 0	98 7	99 2	97 9	99 4	99 0	100 0
- 390	100 0	99 3	99 4	98 2	99 6	99 5	100 0
≤ 400	100 0	99 3	99 6	99 0	99 6	99 5	100 0
No of measurem (N)	141	149	488	623	495	211	87
N as % of no investigated	100 0	100 0	99 4	99 7	99 8	98 6	100 0

1/ % investigated

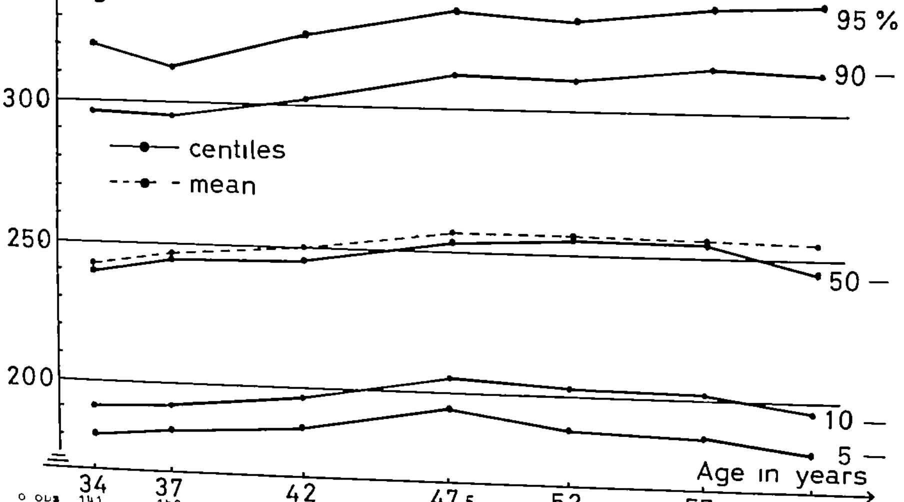


Figure A III 10 health survey in the Reykjavik area Stage I 1967 - 68 - Men diagram showing the mear median and a few centiles of the distributions of total cholesterol values in 7 cohorts (34 yr) (37 yr) (40 42 44 yrs) (46 47 48 49 yrs) (50 51 52 54 yrs) (56 58 yrs) and (61 yr)

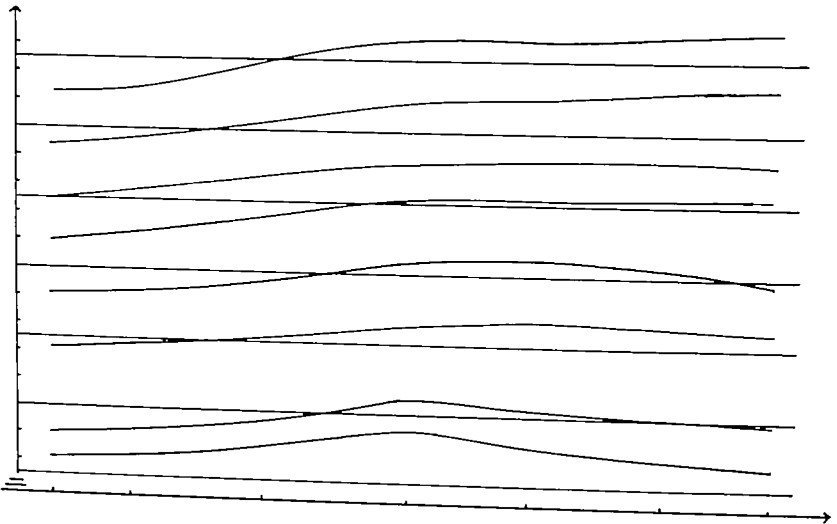


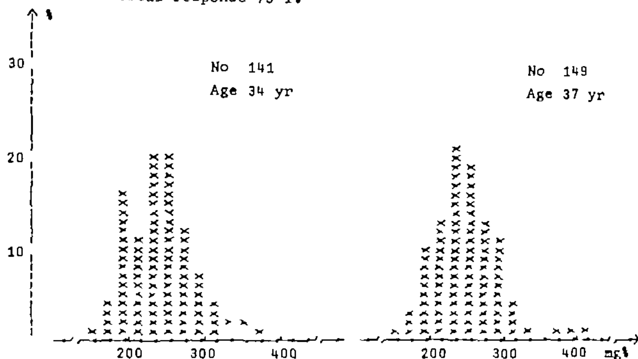
Figure A III 10b Eye fitted curves (Obs highly subjective)5 10 30 50 70 80 90 95% centiles

The coefficients of variation are 0 17 except for the youngest and the oldest cohorts where they are 0 18 The loga rithm of the results is therefore also approximately normally distributed *as shown by the fractile diagrams (Fig A III 13)* In fact the approximation appears to be closer to a lognormal distribution than to a normal distribution

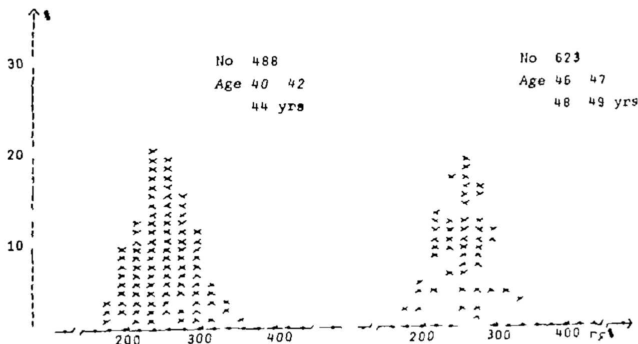
The mean values and all the fractiles appear to increase with age during the interval studied up to the age of 50 The increas is about 10 15 mg% or omewhat less than 1 mg% per year Thus in th 34 to 49 y ar age interval the 95% frac tiles increase from 315 mg% to 330 mg% the 90% fractiles from 295 mg% to 310 mg% means and medians from 240 mg% to 255 mg% the 10% fractiles from about 190 mg% to 205 mg% and the 5% fractiles from about 180 mg% to 190 mg% About the age of 50 there eems to be a change and th means and the fractil s are fairly steady during the next decad except that the lower fractile appear to decrease by somewhat less than 1 mg% per year Thus in th age int rval 50 to 61 y ars the 95% frac- tile are about 330 335 mg% the 90% fractiles are about 310 - 315 mg% th mean and medians are about 55 mg% However the 10% fra til s de rea e from 205 mg% to 195 mg% and the 5% frac- tiles from 190 mg% to 180 mg% during the fifti s

Figure A III 11

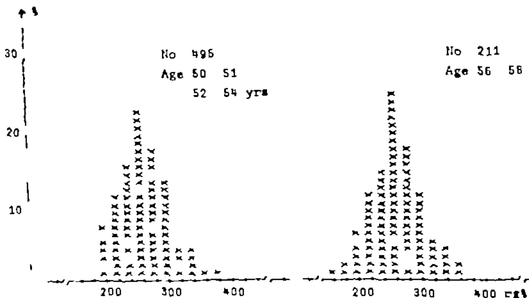
Health survey in the Reykjavik area Stage I, 1967 - 68 - Men
Histograms showing distributions of serum total cholesterol values in men Total response 75 1%[1]



Class width 20 mg%



1/ %investigated



Class width 20 mg%

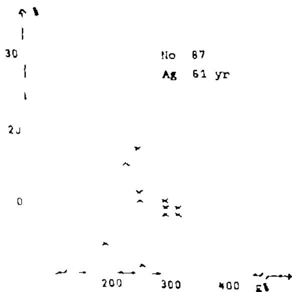


Figure A III 12 health survey in the Reykjavik area Stage I 1967 - 68 - Men
Fractile diagrams of the distributions of serum total cholesterol values in men Total number (No) investigated in all four cohorts 1211 Response 74 7%

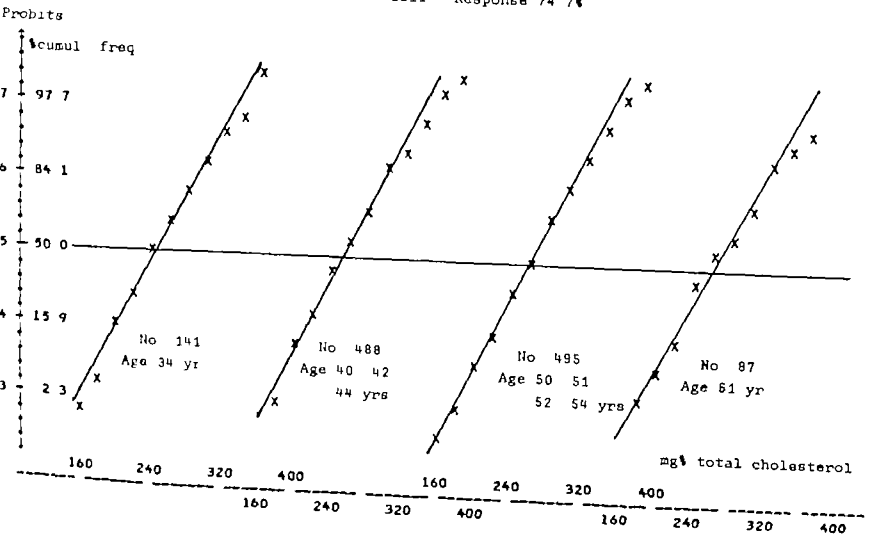
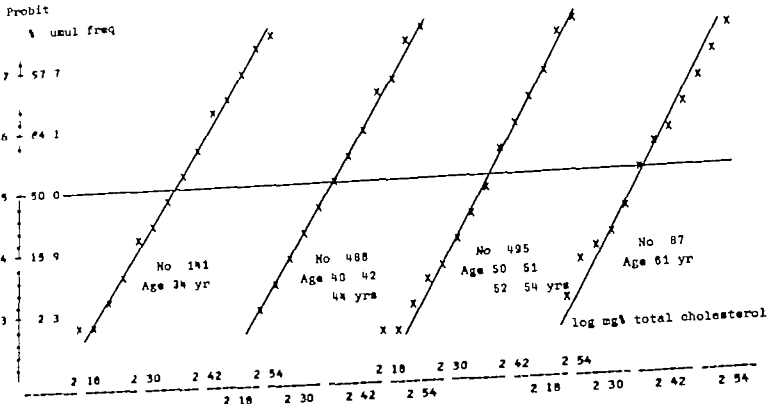
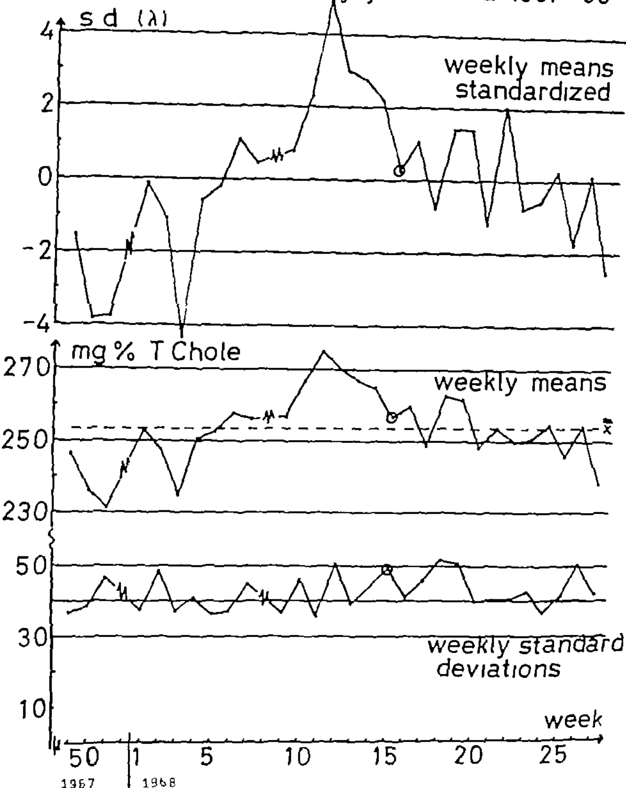


Fig re A III 13 He lth surv y n th Reykjavik area Stage I 1967 68 M n
Fractil diagrams of th di tributio s of the logarithm of s rum total cholesterol valu s in men
Tot l umber (No) in tig ted in ll four cohorts 1211 Re ponse 7% 7%





Obs pr week 45-86 except (O) 20 (⋈) none

Figure A III 14 Health survey in the Reykjavik area Stage I 1967 '68 Men Weekly mean values (x) weekly standard deviation (s) and weekly mean values standardized (λ = (x – x̄) √n/s) of serum total cholesterol values in men n = cts pr week x̄ grand mean

period 240 mg% and 246 mg% respectively (see also the Discussion)

Triglycerides.

Analyses for triglycerides were started in the middle of January 1968 and were continued throughout the period of the survey Triglyceride cont nt was measured in the serum of 1787 participants or from 81 1% of those who attended the clinic the contributions of different age groups being very imilar varying betwe n 76% 85% (Table A III 12) The results are express d as mg% (mg/100 ml) to an a uracy of 1 mg%

From the fractile diagrams and th histograms th results from ach cohort do not appear to be normally distributed (Figs A III 15 16) The distributions are very skew tailing more to right This is also evid nt from Fig A III 18 which shows the mean value to be some 10 mg% higher than the median values and a 3 4 time greater differenc between the 90% 95% fractiles than the 5% 10% fr ctile

All the coeffici nts of variation are about 0 5 The logarithm of the re ults is normally distributed to a very good pproximation as shown by th fractile diagrams (Fig A III 17)

The mean value median values and the lower fractil s all em to be to a good approximation age independent at any ate for th 40 to 60 y ar old age groups Thus th mean values in th se ag group are about 95 mg% the m dian values about 85 mg% nd th 10% and 5% fra tiles are a little le s than 50 mg% nd l ttl more than 35 mg% re p ctively

Th sam does not pply to th high r fra tiles These show a lear in rea from th g of 34 up to 50 y ars but th n ppe t d crea again Thus the 95% fractile incre s s from bout 160 mg% for 36 year old men to 210 mg% ove th n xt 15 y an in re s of a re 3 mg% per year This is followed by d cre of or 30 mg% from 50 to 60 ye rs i e sor 3 mg% pe y r Th ri t on of th 90% fra tile is s mewhat smaller t n th i re se over the irst 15 years is about 30 mg% nd th re e o r the following 10 y rs app ar to be o e 0 g%

Table A III 12 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum triglyceride values in men Total response 75 1%[1/]

Values in mg/100ml (mg%) Class width 20 mg%	Age in years																All age groups
	3[illegible]	37	40	42	44	46	47	48	49	50	51	52	54	56	58	61	
≤ [illegible]	1	0	0	1	1	0	0	1	0	0	0	1	0	0	0	0	5
[illegible]	2	1	1	1	4	0	2	1	0	3	0	1	0	1	0	1	18
[illegible] 40	7	6		2	5	3	7	4	8	2	0	2	6	1	1	4	61
[illegible] 60	17	11	[illegible]	12	7	5	12	7	8	5	6	8	11	6	7	3	131
[illegible]	17	1[illegible]	5	13	15	15	18	11	7	11	13	10	11	10	12	7	185
70	13	11	23	11	1	[illegible]	16	21	12	7	1	7	17	12	7	11	206
[illegible]	12	13	16	20	9	[illegible]	19	15	18	9	17	16	9	20	14	12	238
[illegible]	11	15	14	18	15	15	13	13	6	9	11	13	8	7	5	8	181
[illegible]	[illegible]		15	11	17	3	10	11	8	9	10	8	8	9	6	2	147
[illegible]	7	[illegible]	11	8	8	12	9	12	7	8	3	4	6	7	5	3	125
[illegible]	1		9	6	5	5	6	4	3	5	5	2	9	7	2	3	78
[illegible]	[illegible]		7		11	9	7	6	6	1	3	5	3	3	1	5	88
[illegible]	7		2	4	6	5	3	7	0	4	4	3	4	4	3	3	66
150	1		5	4	3	0	5	5	4	3	0	2	3	3	3	2	49
[illegible]	[illegible]	[illegible]	6	1	5	3	5	4	2	2	0	3	5	0	1	1	37
17[illegible]	1		5	1	3	0	2	2	2	2	1	0	0	1	0	2	26
[illegible]		[illegible]	3	4	2	1	2	3	2	2		2	0	1	0	0	31
19[illegible]		[illegible]	1	0	6	1	3	1	2	2	[illegible]	0	1	2	1	0	22
[illegible]	[illegible]		[illegible]	5	1	2	0	0	0	3	[illegible]	2	1	1	0	2	19
[illegible]	[illegible]	[illegible]	1	1		1	0	2	0	0		2	0	1	0	0	13
[illegible]	[illegible]		0	0	0	3	2	2	0	1	1	0	1	0	1	0	11
[illegible]	0	[illegible]	0	0	0	1	2	1	1	[illegible]	1	2	1	0	0	1	10
240	[illegible]	[illegible]	0	0	1	[illegible]	1	1	1	0	1	1	0	0	0	1	7
[illegible]	[illegible]	1		1	0	[illegible]	[illegible]	2	0	1	[illegible]	0	0	0	0	0	4
[illegible]	[illegible]	3	4	7	1	[illegible]	3	4	3	2	1	2	1	1	1	0	29
Total ( )	1[illegible]	21	1[illegible]	134	140	122	147	140	100	91	101	96	105	97	70	71	1787
N as % of no investigated	[illegible]	1	6 4	81 7	93 9	31 1	[illegible]	9 83 0	78 7	77 7	80 0	75 6	82 6	75 7	81 4	51 6	81 1

1/ % investigated [illegible] stage I started in Nov 67 but the triglyceride measurements began in January 68 [Because] use of the appointment system the 1787 men can be considered as a stratified random [sample] of those [i]nvestigated

Fig A III 19 p 61 shows graphs of the means ($\bar{x}$) and standard deviations (s) for each week throughout the period from the middle of January 1968 up to the beginning of the summer vacation in the beginning of July Also shown is a graph of the standardiz d weekly deviations (λ) from the grand mean ($\bar{\bar{x}}$) These deviations were computer calculated according to the formula $\lambda = (\bar{x} \quad \bar{\bar{x}}) \sqrt{n}/s$ where s is the standard deviation per week and n is the number of results per week The standard deviations appear to be steady throughout the period fluctuating around a value of a little less than 50 mg% The standard deviations of the weekly means vary between 3 6 and 12 6 mg% (most between 5 0 and 8 5 mg%) There is no apparent systematic variation in th results over the period

Table A III 13

Health survey in the Reykjavik area Stage I 1967 - 68 Men
Cumulative distributions of serum triglyceride values in men
Total response 75 1%[1/]

Triglycerides values in mg/100 ml(mg%)	Age in years						
	34	37	40 42 44	46 47 48 49	50 51 52 4	56 58	61
< 20	8	0	5	2	1	0	0
- 30	2 5	8	2 0	1	1 3	6	1 4
- 40	8 5	5 9	4 4	5 1	3 8	1 8	7 0
- 50	22 1	14 9	10 5	11 4	11 5	9 6	11 3
- 60	37 1	23 1	18 6	21 4	23 0	22 8	21 1
- 70	48 3	32 2	9 8	33 4	34 4	34 1	36 6
- 80	59 5	43 0	40 8	47 3	47 4	54 5	53 5
- 90	67 8	55 4	52 3	56 0	57 9	61 7	64 8
- 100	75 4	60 3	62 8	63 9	66 8	70 7	67 6
- 110	81 4	68 6	69 4	71 7	73 5	77 8	71 8
- 1 0	82 2	73 6	74 3	75 2	78 8	83 2	76 1
- 130	88 1	78 5	80 7	80 7	81 9	85 6	83 1
- 140	94 1	87 3	83 6	83 7	85 7	89 8	87 3
- 150	94 7	89 3	86 5	86 4	87 8	93 4	90 1
- 160	94 7	90 1	89 0	89 2	90 3	94 0	91 5
170	95 3	93 4	91 2	90 4	91 1	94 6	94 4
- 180	97 5	95 3	93 4	92 3	92 6	95 2	94 4
- 190	99 1	95 9	95 1	93 7	93 4	97 0	94 4
200	99 1	97 5	96 6	94 1	94 9	97 6	97 2
- 210	99 1	97 5	97 8	94 7	95 9	98 2	97 2
- 2 0	99 1	97 5	97 8	96 1	96 7	98 8	97 2
- 230	99 1	97 5	97	97 0	97 7	98 8	98 5
240	99 1	97 5	98 0	97 6	98 7	98 8	100 0
250	99 1	97 5	98	98 3	98	98 8	100 0
60	99 1	97	98 3	98	98 7	98 8	100 0
270	99 1	97 5	98 3	98 3	99 2	98 8	100 0
280	99 1	97 5	98 5	99 0	99 5	98 8	100
90	99 1	98 3	98 8	99	99 5	99 4	100 0
No of measurem (N)	118	1 1	404	509	312	167	71
N as % of no investigated	83 7	91	83	91	79 1	74 0	81

1/ % investigated [illegible] Stage I started in Nov 67 but the [illegible] rements began in January 68 because [illegible] of the appointment [illegible] the 1787 [illegible] considered as a stratified random [illegible] of the [illegible] investigated

Table A III 14

Health survey in the Reykjavik area Stage I 196 - 68 - Men
Numerical characteristics of the distributions of serum triglyceride values in men Total rosons 75 1%[1/]

Triglyceride values in mg/100ml(mg%)	Age in years						
	34	37	40 42 44	46 47 48 49	50 51 52 54	56 58	61
Mean (x̄)	82 11	97 73	100 17	98 73	96 27	90 86	92 52
Variance	1772 90	2572 12	2589 72	2834 34	2702 30	1832 04	1963 34
s d (s)	42 10	50 71	50 88	53 23	51 98	42 80	44 30
s/x̄	51	52	51	54	54	47	48
5 % centile[2/]	32 92	36 44	37 41	38 44	37 80	40 30	37 78
10 %	37 83	43 56	49 30	47 87	47 60	50 84	47 93
20 %	47 67	56 40	60 32	58 32	57 92	58 99	57 39
30 %	56 10	67 93	70 65	67 41	66 63	67 13	65 28
40 %	63 97	77 21	79 54	76 19	75 24	74 76	72 90
0 %	72 24	85 86	88 43	84 82	83 76	82 02	80 00
0 %	82 50	97 50	99 47	95 02	93 19	89 28	87 10
70 %	93 75	113 33	111 50	108 24	106 04	100 80	105 30
80 %	108 50	133 27	129 28	128 85	126 01	116 04	125 00
90 %	134 00	154 10	165 34	168 40	164 04	141 73	150 10
95 %	152 50	183 50	189 94	213 08	203 30	173 75	195 00
Min	15 00	25 00	13 00	10 00	18 00	30 00	28 00
Max	320 00	310 00	360 00	450 00	510 00	337 00	238 00
Range	305 00	285 00	347 00	440 00	492 00	307 00	210 00
No of measurem (N)	118	121	409	509	392	167	71
N as % of no in stig ted	83 7	81 2	83 3	81 4	79 0	78 0	81 6

1/ % inve tigated Stage I start d in lov 67 but th triglyceride mea urer nts began in January 68 Because of th appointment y t m the 1787 r n can be considered as a stratifi d random arple of those inv stigated

2/ Cutting points below which ar found 5 10 20 etc per cent of the v l s

Table A III 13

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Cumulative distributions of serum triglyceride values in men
Total response 75 1%[1/]

Triglycerides values in mg/100 ml(mg%)	Age in years						
	34	37	40 42 44	46 47 48 49	50 51 5 54	56 58	61
< 20	8	0	5	2	3	0	0
- 30	2 5	8	2 0	1	1 3	6	1 4
- 40	8 5	5 9	4 4	5 1	3 8	1 8	7 0
- 50	22 1	14 9	10 5	11 4	11 5	9 6	11 3
- 60	37 3	23 1	18 6	21 4	23 0	22 8	21 1
- 70	48 3	32 7	29 8	33 4	34 4	34 1	36 6
- 80	58 5	43 0	40 8	47 3	47 4	54 5	53 5
- 90	67 8	55 4	52 3	56 6	57 9	61 7	64 8
- 100	75 4	60 3	62 8	63 9	66 8	70 7	67 6
- 110	81 4	68 6	69 4	71 7	73 5	77 8	71 8
- 120	87 2	73 6	74 3	75 2	78 8	83 2	76 1
- 130	88 1	78 5	80 7	80 7	81 9	85 6	83 1
- 140	94 1	84 3	83 6	83 7	85 7	89 8	87 3
- 150	94 9	89 3	85 5	86 4	87 8	93 4	90 1
- 160	94 9	90 1	89 0	89 2	90 3	94 0	91 5
- 170	95 8	93 4	91 2	90 4	91 1	94 6	94 4
- 180	97	95 9	93 4	92 3	92 6	95 2	94 4
- 190	99 1	95 9	95 1	93 7	93 4	97 0	94 4
- 200	99 1	97 5	96 6	94 1	94 9	97 6	97 2
- 210	99 1	97 5	97 8	94 7	95 9	98 2	97 2
- 220	99 1	97 5	97 8	96 1	96 7	98 5	97 2
- 230	99 1	97 5	97 8	97 0	97 7	98 8	98 5
- 240	99 1	97 5	98 0	97 6	98 2	98 8	100 0
- 250	99 1	97 5	98	98 1	98 5	98 8	100 0
- 260	99 1	97	98 3	98 2	98 7	98 8	100 0
- 270	99 1	97 5	98 3	98 9	99 2	98 8	100 0
- 280	99 1	97 5	98 5	99 0	99 5	98 8	100 0
- 290	99 1	98 3	99 8	99	99 5	99 4	100 0
No of measurem (N)	115	171	409	07	312	157	71
N as % of no investigated	83 7	91 2	83	91 4	79 3	73 0	81 8

1/ % investigated Stage I started in Nov 67 but the TG m a urements began in January 68 Because of the appointment sy tem the 1787 men can be considered as a stratified random sample of those investigated

↑%

30

20

10

No 392
Age 50 yr

50 150 250

No 167
Age 56 yr

50 150 250 mg%

Class width 20 mg%

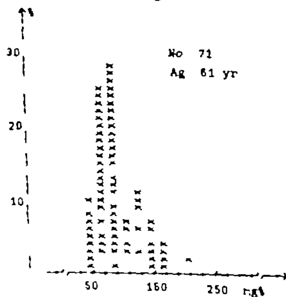


Figure A III 15

Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Histograms showing distributions of serum triglyceride values in men

Total response 75 1%

↑%

30

No 118

Age 34 yr

No 121

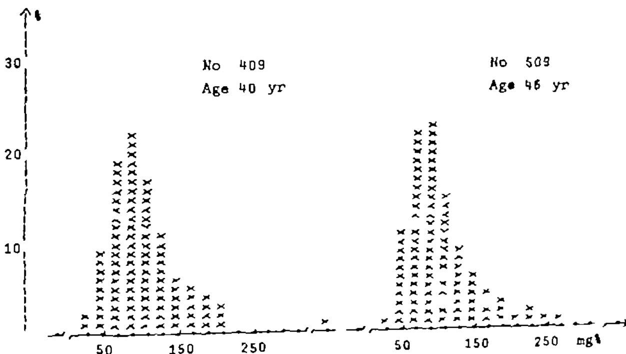
Age 37 yr

20

10

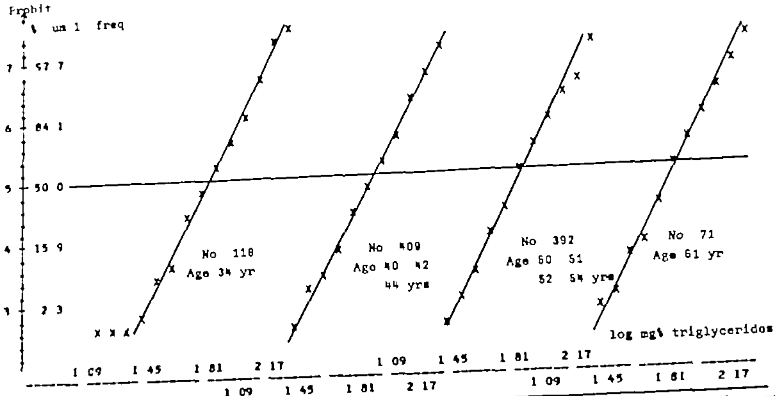
50 150 250 50 150 50 mg%

Class width 20 mg%



1/ % investigated Stage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 1787 men can be considered as a stratified random sample of those investigated

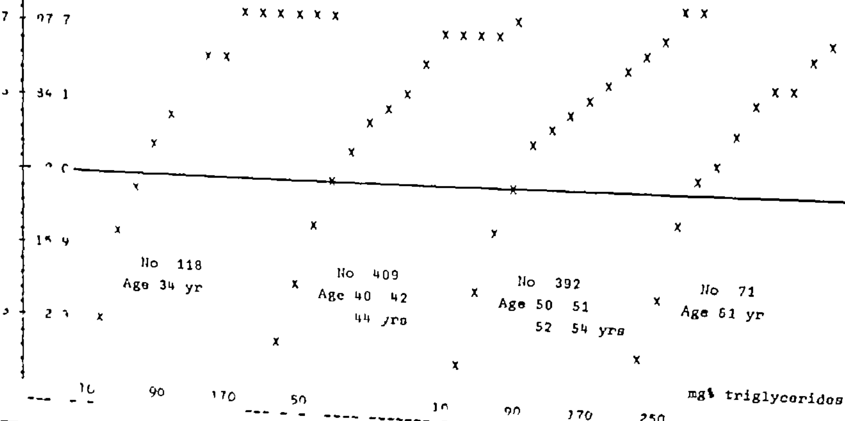
Fig re A III 17 l ltl s rv y in th Roykja ik area Stage I 1967 68 Men
Fr tile d gr of th d tr b t ns of th log rithm of erum trigly oride values in men Total
nurb (H) i vestig t d i ll four cohorts 890 R sponse 74 7%[1]



1/ % investigated St ge I started in Nov 67 but the triglyceride measurements began in January 68 B cause of the appointment system the 990 men can be considered as a stratified random sample of those investigated

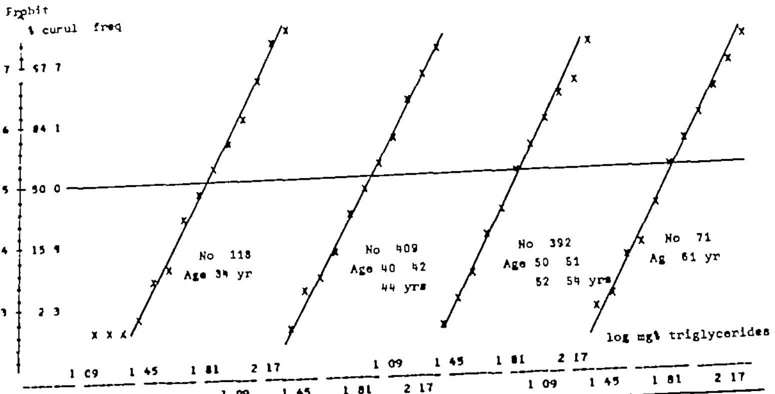
Figure ?/III 10 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Fractile diagrams of the distributions of serum triglyceride values in men investiagated in all four cohorts 990 Total number (No) Response 74 7%[1/]



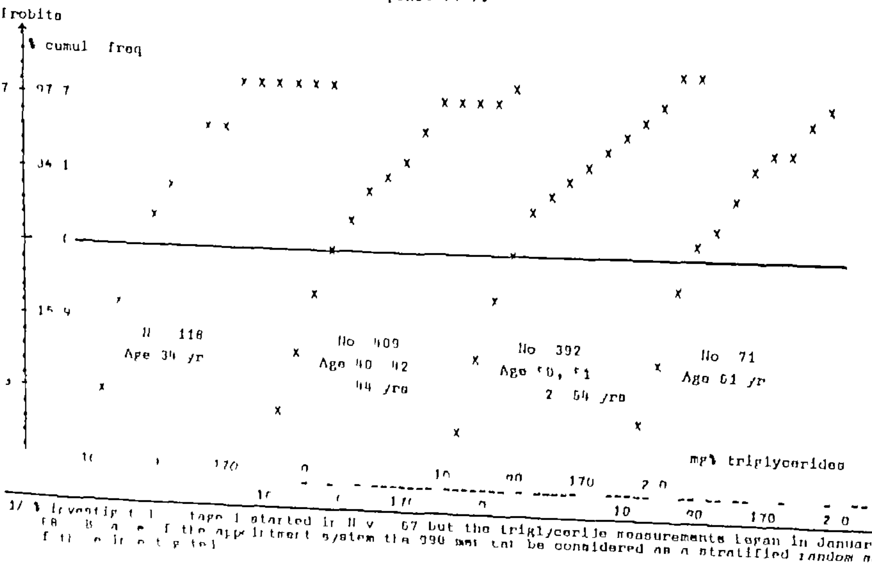
1/ % investigated tage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 990 men can be considered as a stratified random sample of those investigated

Fig re A III 17. H lth s y in th Reykj ik area St ge I 1967 68 Men Fractil di g s f th d trib ti ns of th log rithm of s rum trigly rid values in men Total number (No) in t gat d n ll f ur cohorts 990 Respons 74 7%[1/]



1/ % investigated Stage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 990 men can be considered as a stratified random sample of those investigated

Figure A III 16 Health survey in the Reykjavik area Stage I, 1967 - 68 - Men
Fractile diagrams of the distributions of serum triglyceride values in men Total number (No) investigated in all four cohorts 990 Response 74 7%[1/]



1/ % investig ... Stage I started in Nov 67 but the triglyceride measurements began in January ... the appointment system the 990 men can be considered as a stratified random sample

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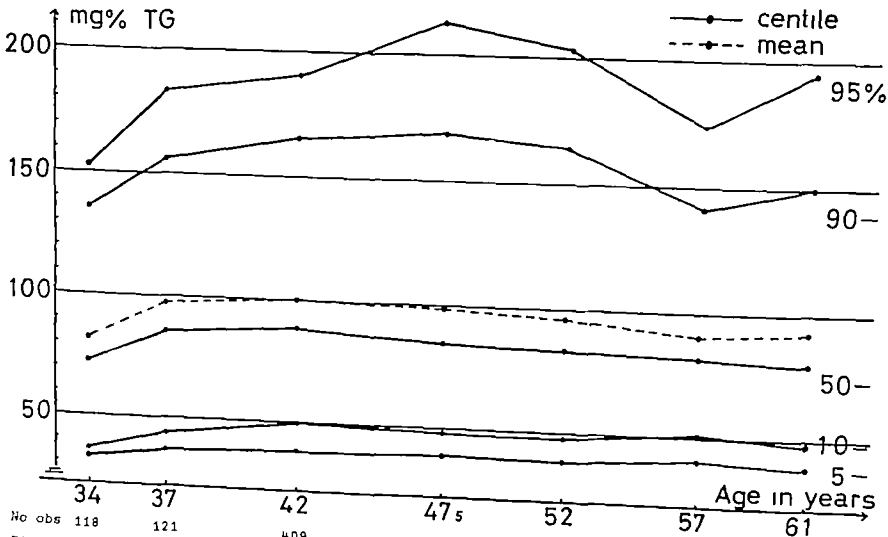
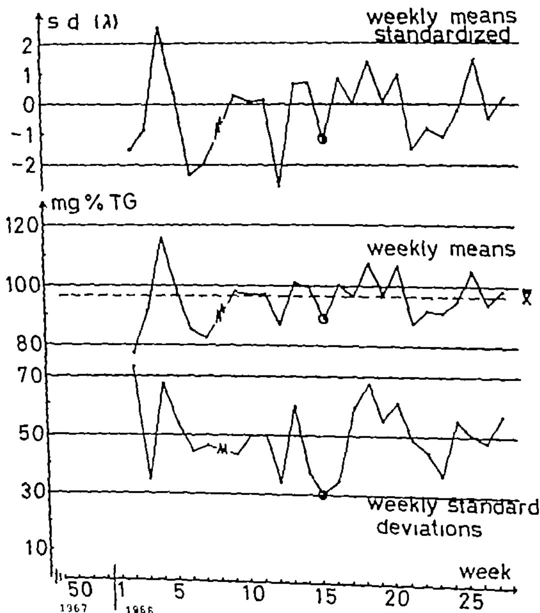


Figure A III 18 Health survey in the Reykjavik area Stage I 1967 – 68 – Men
Diagram showing the mean median and a few centiles of the distributions of serum triglyceride values in 7 cohorts (34 yr) (37 yr) (40 42 44 yrs) (46 47 48 49 yrs) (50 51 52 54 yrs) (56 58 yrs) and (61 yr)

Health survey in the Reykjavik area 1967-'68



b F we k 32 86 except (o) 20 ( ) none

Fig re III 19 I alth rvey in the Feykjavik area tag I 1967-
 w kly mea v l ($\bar{X}$) we kly standard deviations (s)
nd kly gr n alues standardized (λ ($\bar{X}$) √n/s) of s rum tri
gl r d (TG) v lues in r n
= no f obs pr week $\bar{\bar{X}}$ = gr nd ean

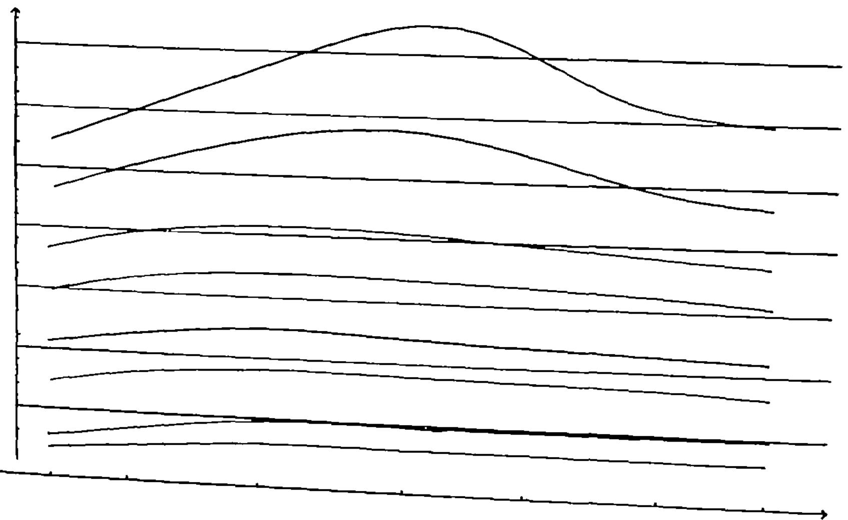


Figure A III 18b Lye-fitted curves (Obs Highly subjective) 5 10 20 30 50 70 80 90 95% centiles

Beta lipoproteins, total cholesterol and triglyceride correlations

There is a positive correlation between values for beta-lipoproteins and total cholesterol (Tables A III 15 21) The correlation coefficients decrease with increasing age and their valu s are much the same whether or not the logarithms of the results are used The correlation coefficients decrease from about 0 7 at the age of 34 to about 0 5 at the ag of 61

A correlation i also seen from Fig A III 21 (p 64) which is based on th above mention d tabl s The figure shows how the means of the results of beta lipoprotein measurements increase with increasing total cholesterol concentration in the cohorts 40 44 45 49 and 50 54 years The results of the beta lipoprotein measurements in each of these cohorts were grouped a cording to the total cholesterol values and mean v lues for b ta lipoproteins for each group calculated The mean values appear to increa e evenly or by about 0 09 mm IC per 10 mg% of total cholesterol at any rate up to a cholesterol valu f 250 mg% For higher cholesterol values the rate of incre se in IC seems to be less

A very similar correlation is seen for the results for beta lipoproteins and triglycerides (Tables A III 22 28) The correlation coefficients do however appear to decrease more with ag or from abo t 0 7 to about 0 4 In Fig A III 22 it can b s en that th mean values for beta lipoproteins increase by ab ut 0 09 mm IC per 10 mg% of triglycerides at any rat up to a triglyc ride valu of 120 mg% For higher TG values there s ems to b littl if any incre s in IC

The correlatio between total cholesterol and triglyceride lues quite different The correlation coefficients are positi but low or about 0 1 and appear to b virtually age ind pend nt I Fig A III 23 it can be seen that the mean lues for triglyc rid s increa almost linearly with increas ng t t l hol sterol values or by about 4 mg% per 10 mg% of t t l hol st rol

Table A III 36 p 81 shows the partial correlation ffi ts for the v lu s of these three serum lipids Here tr pa ti l corr lation c efficients between total cholesterol nd triglycer des appe r to be none (zero)

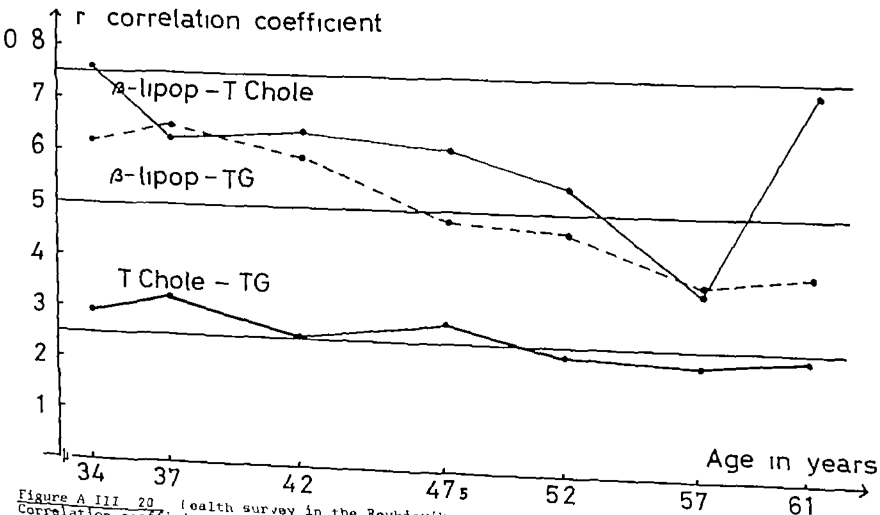


Figure A III 20 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Correlation coefficients of β-lipoprotein and total cholesterol β-lipoprotein and triglycerides and total cholesterol and triglycerides plotted against mean age of 7 cohorts- (34yr) (37 yr) (40 42 44 yrs) (46 47 48 49 yrs) (50 52 54 yrs) (56 58 yrs) and (61 yr) - Based on Tables A III 15 35

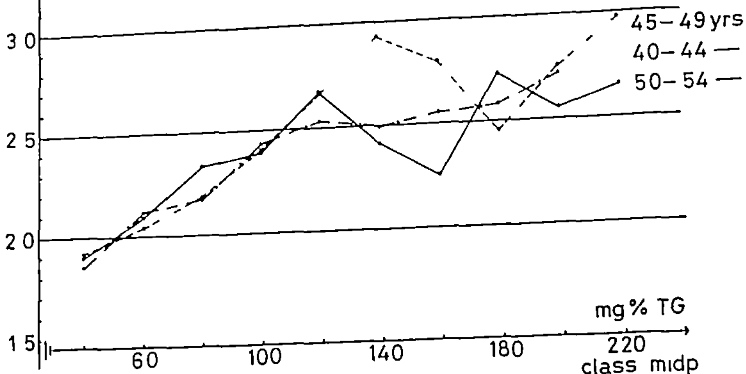


Figure A III 22 Health survey in th Reykjavik area Stage I 1967 - 68 - Men
Mean v lues of β lipoproteins plotted agains grouped triglyceride values within three cohorts
Based on Tables A III 22 28

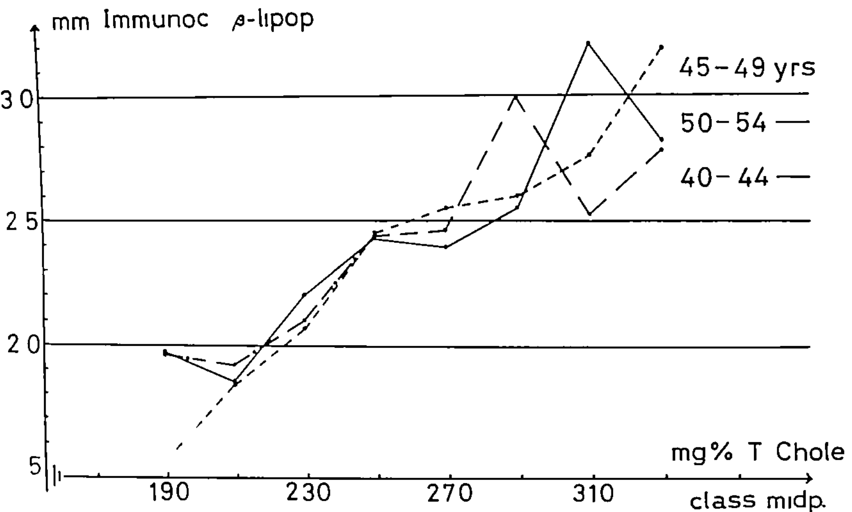


Figure A III 21 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Mean values of β-lipoproteins plotted against grouped total cholesterol values within three cohorts - Based on Tables A III 15-21

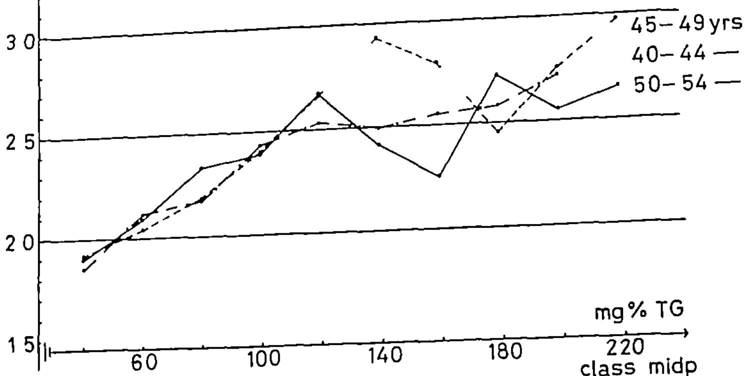


Figure A III 22 Health surv y in the Reykjavik area Stage I 1967 - 68 Men
H an values of β lipoproteins plotted agains grouped triglyceride values within three cohorts
B sed on Tables A III 22 28

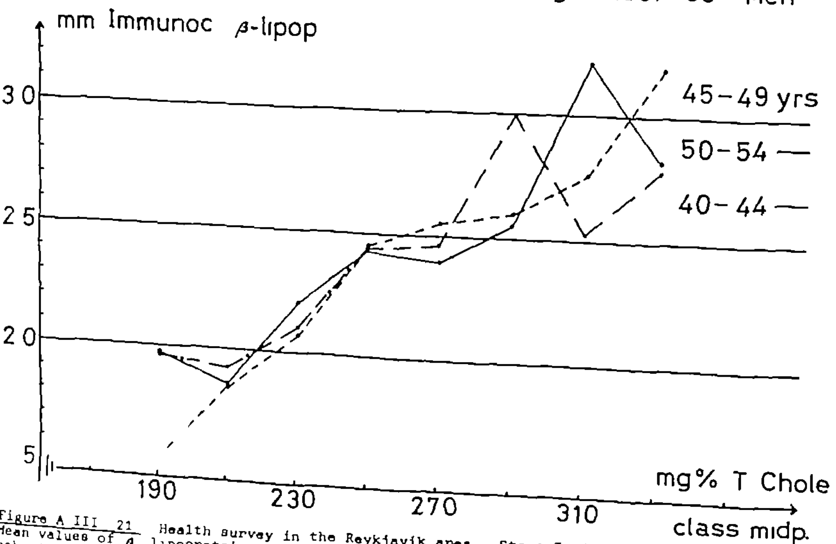


Figure A III 21 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Mean values of β lipoproteins plotted against grouped total cholesterol values within three cohorts Based on Tables A III 15-21

T ble A III 15 le lth r y th R ykja k re Stag I 1967 68 M n
Fr q y t ll f rum B lipcpr t alues d rum total hol sterol values in men
Numb r f me 33 Ag 34 y R po e 71 6%[1/]

B lipop ro Im n c Cl midp	Total cholesterol value in mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	≤150	170	190	10	230	250	270	290	310	330	350	370	3 0	410	430	≥450
5 35																
1 05																
1 25																
1 45			1													
1 65			1													
1 85			1	3	2											
2 05			1	1	2	1	1									
2 25					2	[illegible]										
2 5				1	1			1								
2 5							1		1							
2 35					1		1	1	1							
3 05										1						
3 5								1								
3 45								1								
3 65																
3 85																
4 05																
5																
4 45																
≥ 4 5																

B lipoprot in values (x)				Correlation coefficient		Total cholesterol values (y)			
M an x	2 22	d x	433	r(x y)	7589	Mean y	244 06	S d y	40 23
Mean l g x	333	d log x	1127	r(log x log y):	7734	M an log y:	2 382	S d log y:	0717

1/ % inv stigated tage I start d in Nov 1967 but the β lipoprot in measurements began in May 1968 Bec use of the ppointment system the 33 men can be considered as a r ndom sample of thos investigated

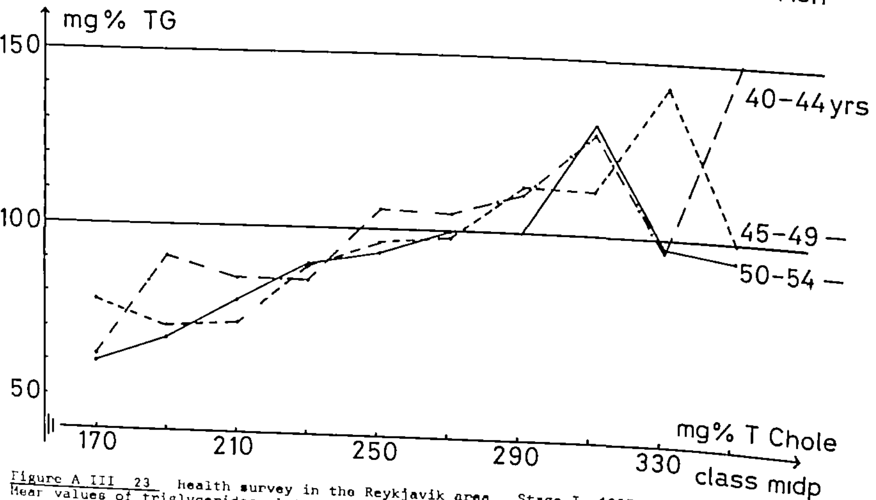


Figure A III 23 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Mean values of triglycerides plotted against grouped total cholesterol values within three cohorts Based on Tables 29 35

T bl A III 15 | lth r y l th R ykja ik rc Stag I 1967 68 M n
Fr q y t ll f s rum B l p-prot l s and s rum total cholest rol alu s in men
N ber f m 33 Ag 34 y R spo o 71 6%[1/]

B lipop nm Imm noc Cl midp	≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	43	≥45
	Tot l cholest rol v lu s i mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
.85																
1 05																
1 25																
1 45			1													
1 65			1													
1 85			1	1	2											
2 05			1	1	2	1	1									
2 25					2	1										
2 45				1	1			1								
2 65							1		1							
2 85					1		1	1	1							
3 05										1						
3 25								1								
3 45								1								
3 65																
3 85																
4 05																
4 25																
4 45																
≥ 4 65																

B-lipoprotein alu s (x)				Correlation coeffici nt		Total cholesterol values (y)			
M an x	?	d x	433	r(x y)	7539	M an y :	244 06	S d y	40 23
Mean log x	333	d log x:	1127	r(log x log y)	7734	Mean log y:	2 382	S d log y:	0717

1/ % inv stigated Stag I start d in Nov 1967 but the β lipoprotein measurements began in May 1968 Bec us of the appointment system the 33 men can be considered as a random sample of those investigated

Table A III 16 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Frequency table of serum B-lipoprotein values and serum total cholesterol values in men
Number of men 38 Age 37 years Response 71 3%[1/]

B lipop mm Immunoc Cl midp	Total cholesterol values in mg/100ml (mg%) — Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
≤ .85																
1.05						1										
1.25																
1.45		1	1													
1.65			2			1										
1.85			1	1		1	1									
2.05		1														
2.25					2	1	4	1								
2.45					3	1	1	2								
2.65							1									
2.85						1										
3.05							7		1							
3.25										1						
3.45						1										
3.65																
3.85							1									
4.05																
4.25																
4.45									1							
> 4.65																

B-lipoprotein values (x) — Mean x 2 30, S d x 684; Mean log 351, S d log x 1243

Correlation coefficient — r(x y) 6278; r(log x log y) 5285

Total cholesterol values (y) — Mean y 251 89; Mean log y 2 397; S d y 35 85; S d log y 0654

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 38 men can be considered as a random sample of those investigated

Men

Tbl A III 17 Health survey in the Reykjavik area Stage I 1967 68 Men

Frequency table of serum B lipoprotein values and serum total cholesterol values in men

Number of men 146 Age 40 42 44 years Response 76 4%[1/]

B lipoprotein Innu oc	Total cholesterol values in mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
Cl midp	s150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
5 35																
1 05																
1 25			1				1									
1 45				1												
1 65	1	2	3	7	3											
1 85		1	6	8	4		1									
2 05			5	2	11	4	4	1								
2 25			2	4	6	7	9	1		2						
2 45			1		1	3	7	1	2	1						
2 65						1	3	1	1			1				
2 85			1		1	3	2	2		1	1					
3 05					1	3	1	2								
3 25						1	1			1	2					
3 45																
3 65							1			1						
3 85																
4 05																
4 25								1								
4 45								1								1
- 4 65																

B-lipoprotein values (x)	Correlation coefficient	Total cholesterol values (y)
Mean x 2 29 S d x : 549	r(x y) 6426	Mean y : 247 15 S d y : 45 28
Mean log x: 349 S d log x 0963	r(log x log y): 6470	Mean log y 2 386 S d log y 0769

1/ % investigated Stage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Because of the appointment system the 146 men can be considered as a random sample of those investigated

Table A III 16 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum total cholesterol values in men

Number of men 38 Age 37 years Response 71 3%[1/]

B lipop mm Immunoc	Total cholesterol values in mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
Cl midp	≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
≤ 85																
1 05						1										
1 25																
1 45		1	1													
1 65			2			1										
1 85			1	1		1	1									
2 05		1														
2 25					2	1	4	1								
2 45					3	1	1	2								
2 65							1									
2 85						1										
3 05							2		1							
3 25										1						
3 45						1										
3 65																
3 85							1									
4 05																
4 25									1							
4 45																
4 65																

B lipoprotein values (x)

Mean x 2 30 S d x 684

Mean log x 361 S d log x 1743

Correlation coefficient

r(x y) 6278

r(log x log y) 5285

Total cholesterol values (y)

Mean y 251 89 S d y 35 85

Mean log y 2 397 S d log y 0654

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 38 men can be considered as a random sample of those investigated

T bl A III 17 H l h s rv y n the R ykja ik ar a Stage I 1967 68 M n
Freq on y tabl f serum B l poprot i lu s and serum total holest rol values in men
Number f n 146 Ag 40 42 44 y ars Respon 75 4%[1/]

B lipop an Imm noc Cl midp	Total hol sterol valu s in mg/100ml (mg%) — Class midpoint minus 0 5 mg % (Class width 20 mg %) 150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
.85																
1 05																
1 25			1				1									
1 45				1												
1 65	1	2	3	7	3											
1 85		1	6	8	4		1									
2.05			5	2	11	4	4	1								
2 25			2	4	6	7	8	1		2						
2 45			1		1	3	7	1	2	1						
2 65						1	3	1	1			1				
2 85			1		1	3	2	2		1	1					
3 05					1	3	1	2								
3 25						1	1			1	2					
3.45																
3 65							1			1						
3 85																
4 05																
4 25								1								
4 45								1								1
4 65																

β-lipoprotein values (x)				Correlation coefficient		Total cholesterol values (y)			
Mean x	2 29	S d x	549	r(x y)	6426	Mean y	247 15	S d y	45 28
Mean log x	349	S d log x:	0963	r(log x log y):	6470	Mean log y:	2 386	S d log y	0769

1/ % investigated Stage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Because of the appointment system the 146 men can be considered as a random sample of those investigated

Table A III 18 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Frequency table of serum B-lipoprotein values and serum total cholesterol values in men
Number of men 161 Age 46 47 48 49 years Response 77 3%[1/]

B lipop mm Immunoc Cl midp	Total cholesterol values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
≤ 85			1	1												
1 05																
1 25			1													
1 45		2	4	1	1		1									
1 65			1	7	2	1		1								
1 85		1	2	6	5	3										
2 05			1	5	12	7	6	3	2							
2 25				1	4	7	5	4	1		1			1		
2 45				2	1	5	3	1	1							
2 65						5	3				1					
2 35					1	3	3	2	1	2						
3 05					1	1	8	1	1		2					
3 25							1	3								
3 45						1										
3 65																
3 85						1		1		1						
4 05						1								1		
4 25																
4 45																
4 65									1							1

B lipoprotein values (x)
Mean x 2 32 S d x 646
Mean log x 349 S d log x 1171

Correlation coefficient
r(x y) 6175
r(log x log y) 6331

Total cholesterol values (y)
Mean y 254 57 S d y 44 29
Mean log y 2 400 S d log y 0718

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 161 men can be considered as a random sample of those investigated

T bl A III 19 H lth ur ey in the R ykja ik are St g I 1967 88 Men

Freq cy t bl f s rum B l poprot in value and s rum total cholesterol valu s in m n

Number of n n 116 Age 50 51 52 54 y ars Response 75 7%[1/]

B lipop m Imo n c Cl midp	Total cholest rol valu s in mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
85																
1 05																
1 25																
1 45		1		2												
1 65			2	2	3											
1 85			2	8	4	4	1									
2 05			4	6	8	5	5	7		1						
2 25			2		2	2		2								
2 45					6	7	4	3		1						
2 65								2	1							
2 85					4	1	3	1	1							
3 05						3	1	1		3		1				
3 25										1						
3 45								1								
3 65									2							
3 85																
4 05																
4 25																
4 45																
4 65						1										

B lipoprotein values (x)	Correlation coefficient	Total cholesterol values (y)
Mean x : 2 30 S d x 552	r(x y) : 5504	Mean y : 248 19 S d y 38 78
Mean log x 350 S d log x: 0941	r(log x log y) 6106	Mean log y: 2 390 S d log y 0669

1/ % investigated tage I started in Nov 1968 but the β lipoprotein measurement started in May 1968 Because of the appointment system the 116 men can be considered as a random sample of those investigat d

able A III 20 *Health survey in the Reykjavík area* Stage I 1967 - 68 - Men
requency table of serum B-lipoprotein values and serum total cholesterol values in men
umber of men 43 Age 56 58 years Response 74 3%[1/]

-lipop mn mmunoc 1 midp	Total cholesterol values in mg/100ml (mg%) — Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
≤ 85																
1 05																
1 25	1															
1 45						1										
1 65			1	2												
1 85					4		1									
2 05				3	4	1	2	2								
2 25						2	1	2	2	1						
2 45						3	1									
2 65				1			2									
2 85				1		1	1									
3 05																
3 25						1										
3 45																
3 65																
3 85						1		1								
4 05																
4 25																
4 45																
4 65																

B lipoprotein values (x) — Mean x 2 24, Mean log x 341; S d x 517, S d log x 0936

Correlation coefficient — r(x y) 3580; r(log x log y) 4432

Total cholesterol values (y) — Mean y 248 00; Mean log y 2 390; S d y 35 03; S d log y 0633

1/ % investigated ... tage I started in Nov 1967 but the B-lipoprotein measurements began in May 1968 Because of the appointment system the 43 men can be considered as a random sample of those investigated

T bl A III 21 H alth rv y th R ykjavik r a Stage I 1967 88 Men

Freq y t bl f rum B lipoprot in al and s rum total cholesterol valu s in men

Number f r 19 Ag 61 y ar Re ponse 69 6%[1/]

B lipop Immunoo Cl midp	Total cholesterol values in mg/100ml (mg%) Cl as midpoint minus 0 5 mg % ≤150	170	190	210	230	250	270	290	310	330	350	370	390	410	430	≥450
85																
1 05																
1 25		1														
1 45																
1 65																
1 85				2	1		1									
2 05			1	2	2	1										
2 25					2	3	1			1						
2 45								1								
2 65																
2 85																
3 05																
3 25																
3 45																
3 65																
3 85																
4 05																
4 25																
4 45																
4 65																

B lipoprotein values (x)				Corr lation coefficient		Total cholesterol values (y)			
Mean x	2 04	S d x	257	r(x y)	7282	Mean y	239 42	S d y	36 63
Mean log x	306	S d log x	0595	r(log x log y)	7562	Mean log y	2 374	S d log y	0663

1/ % investigat d Stage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Because of the appointment syst m the 19 men can be considered as a random sample of those in estigated

Table A III 22 health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 33 Age 34 years Response 71 6%[1/]

B lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85		1														
1 05																
1 25																
1 45			1													
1 65						1										
1 85	1	4	3													
2 05		1	1	1	1		1		1							
2 25		2		2												
2 45			1	1		1										
2 65					1	1										
2 85			1	1		1			1							
3 05									1							
3 25							1									
3 45																1
3 65																
3 95																
4 05																
4 25																
4 45																
≥ 4 65																

B lipoprotein values (x)

Mean x 2 22 S d x 533
Mean log x 333 S d log x 1127

Correlation coefficient
r(x y) 6207
r(log x log y) 5586

Triglyceride values (y)
Mean y 91 79 S d y 59 71
Mean log y 1 891 S d log y 2465

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 33 men can be considered as a random sample of those investigated

Stag I 1987 68 Men

<u>T bl A III 23</u> H lth sur y th R ykj vik r Stag I 1987 68 Men

F eq n y t bl of rum B lipoprot in alu s and s rum triglyc rid values in men[1/]

Number f men 38 Ag 37 years R sponse 71 3%

B lipop rn Immunoo Cl midp	Triglyc rid alues in mg/100ml (mg%) Clas midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85																
1 05				1												
1 25																
1 45		2														
1 65		1	2													
1 85		2	1	1												
2 05				1			1			1						
2 25			1	2		2	2	1								
2 45				1	3		1		1	1						
2 65					1											
2 85							1									
3 05				2		1										
3 25				1												
3 45														1		
3 65															1	
3 85															1	
4 05																
4 25							1									
4 45																
≥4 65																

B-lipoprot in valu s (x)				Correlation coefficient		Triglycerid values (y)			
Mean x :	2 39	S d x	684	r(x y) :	6916	Mean y :	116 68	S d y	68 85
Mean log x	361	S d log x:	1243	r(log x log y)	6610	Mean log y:	2 003	S d log y	2353

1/ % investigated Stage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Because of the appointment system the 38 men can be considered as a random sample of those investigated

Table A III 22 health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 33 Age 34 years Response 71 6%[1/]

B-lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85		1														
1 05																
1 25																
1 45			1													
1 65						1										
1 85	1	4	3													
2 05		1	1	1	1		1		1							
2 25		2		2												
2 45			1	1		1										
2 65					1	1										
2 85			1	1		1			1							
3 05									1							
3 25							1									
3,45																1
3 65																
3 85																
4 05																
4 25																
4 45																
> 4 65																

B lipoprotein values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	2 22	S d x	533	r(x y)	6207	Mean y	91 79	S d y	59 71
Mean log x	333	S d log x	1127	r(log x log y)	5586	Mean log y	1 891	S d log y	2465

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 33 men can be considered as a random sample of those investigated

Tbl A III 23 l lth sur y i th R ykj ik re St ge I 1967 68 Men
Freq n y t bl of s run B-lipoprotein v lu and serum triglyceride valu s in men
Number of me 38 Ag 37 year Response 71 3%[1/]

B lipop nm Immunoc Cl midp	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
	Triglycerid value in mg/100ml (mg%) — Class midpoint min s 0 5 mg % (Class width 20 mg %)															
≤ 85																
1 05				1												
1 25																
1 45		2														
1 65		1	7													
1 85		?	1	1												
2 05				1			1			1						
2 25			1	?		2	2	1								
2 45				1	1		1		1	1						
2 5					1											
2 85							1									
3 05				?		1										
3 25				1												
3.45														1		
3 65															1	
3 95															1	
4 05																
4 25							1									
4 45																
≥4 65																

lipoprotein values (x)	Correlation coefficient	Triglyceride values (y)
n x : 2 39 S d x : 684	r(x y) : 6516	Mean y : 116 68 S d y : 68 85
ean log x 361 S d log x: 1243	r(log x log y): 6610	Mean log y 2 003 S d log y: 2353

1/ % investigated Stage I started in Nov 1967 but th β lipoprotein measurements began in May 1968 Becaus of the appointment system tho 38 men can b considered as a random sample of those inv stigat d

Table A III 24 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 146 Age 40 42 44 years Response 75 4%[1/]

B-lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤ 20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥ 320
≤ 85																
1 05																
1 25	1		1													
1 45			1													
1 65	1	5	4	1												
1 85		4	4	9	5	1	1									
2 05		3	3	10	5	4	1	1								
2 25		1	9	6	6	2	2		1	3						
2 45			2	6	2	4	1	1								
2 65			1	2	1	1			2							
2 85					1	7	3	2	1	2						
3 05			1		5		1									
3 25			1		1	1				2						
3 45																
3 65				1	1											
3 85																
4 05																
4 25																
4 45																
> 4 65						1										1
																1

B lipoprotein values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	2 29	S d x	549	r(x y)	5978	Mean y	99 83	S d y	50 62
Mean log x	349	S d log x	0963	r(log x log y)	5948	Mean log y	1 953	S d log y	

1/ % investigated Stage I started in Nov 1967 but the B-lipoprotein measurements began in May 1968 Because of the appointment system the 146 men can be considered as a random sample of those investigated 1968

A II — I t F ykj k re t ge I 1967 68 H n

1 q y t tI f b l pcprot n 1 nd s rum triglycerid values in mon

Numbe f 159 Ag 4C 47 48 49 y R pon 77 3%[1/]

β lipo p (Class midp)	Trigly id lu s i mg/100ml (mg%) (Cl n dpo nt si s 0 5 mg % (Class width 20 mg %)) 2	40	60	80	100	120	140	160	180	200	2 0	240	260	280	30	≥ 20
1 45			1		1											
1 05																
1 25			1													
1 45		2	4													
1 65		4	3	1	2											
1 85		4	6	4		1			1							
2 05		4	13	17	3		1		1		2					
2 25		1	8	6	2	4	1	1	1							
2 45		1	1	1	5	3			2							
2 65				3	1	2	1			1		1				
2 85		1	3		1			1		1	1					
3 05					3	2	3	2	2							
3 25				2		1					1					
3 45							1									
3 65																
3 85					1		1							1		
4 05						1							1			
4 25																
4 45																
4 65	1										1					

lipoprot in 1 s (x)				orrelation coefficient		Triglyceride values (y)			
n x	2 37	d x	645	r(x y)	4797	Mean y	95 77	d y	49 57
n log x	351	d log x	1169	r(log x log y)	4547	Mean log y	1 931	S d log y	2058

1/ % in otigat d tage I started in Nov 1967 but the β lipoprotein measurements began in May 1968 Be ause of the appointment system th 159 men can be considered as a random sample of those inv stigated

Table A III 24   Health survey in the Reykjavik area   Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 146   Age 40 42 44 years   Response 75 4%[1/]

B-lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85																
1 05																
1 25	1		1													
1 45			1													
1 65	1	5	4	1												
1 85		4	4	9	5	1	1									
2 05		3	3	10	5	4	1	1								
2 25		1	9	6	6	2	2		1	3						
2 45			2	6	2	4	1	1								
2 65			1	2	1	1			2							
2 85					1	7	3	2	1	2						
3 05			1		5		1									
3 25			1		1	1				2						
3 45																
3 65				1	1											
3 85																
4 05																
4 25																
4 45																
> 4 65						1										1 ↑

B lipoprotein values (x)

Mean x 2 29   S d x 549
Mean log x 349   S d log x 0963

Correlation coefficient
r(x y) 5978
r(log x log y) 5948

Triglyceride values (y)
Mean y 99 83   S d y 50 62
Mean log y 1 953   S d log y

1/ % investigated   Stage I started in Nov 1967 but the B lipoprotein measurements began in May 1968   Because of the appointment system the 146 men can be considered as a random sample of those investigated

l A III 7 | 1 tr R y}j k r a St ge I 1987 68 M n

Freq y t bl of un B l pop ot i alu and rum triglyceride valu s in men

Aurbe f 42 Ag 56 68 y r R spons 74 3%[1/]

B lipop nn I mu oc Cl midp	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
	Triglycerid v lue in mg/100ml (mg%) — I midpoi t minus 0 5 mg % (Class width 20 mg %)															
- 85																
1 05																
1 25			1													
1 45			1													
1 65		1			1											
1 85			1	2	1	1										
2 05			4	3	3	2										
2 2			4	7					1	1						
2 45			1	2	1											
2 65					1	1			1							
85			1	1	1											
3 05																
3 25						1										
3 45																
3 5																
3 85							2									
4 05																
4 25																
4 45																
4 5																

B lipoprot in v luos (x)		Correlation coefficient		Triglyceride values (y)	
Mean x : 2 76	S d x 516	r(x y)	3756	Mean y : 92 98	S d y : 36 75
Mean log x 343	S d log x 0931	r(log x log y)	3789	Mean log y 1 940	S d log y 1536

1/ % in estigated Stage I started in Nov 1987 but the β lipoprotein measurements began in May 1988 Beca s of the ppointment system the 42 men c n be considered as a random sample of thos inv stigated

Table A III 26 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 114 Age 50 51 52 54 years Response 75 7%[1/]

B-lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85																
1 05																
1 25																
1 45		2	1													
1 65		1	4	1	1											
1 85	1	5	8	2	2	1										
2,05	1	6	10	9	1		2	1								
2 25			2	1	2				1	1	1					
2 45		1	3	6	1	5	1	1		2	1					
2 65			1				1				1					
2 85			2	2	1	2	1		1		1					
3 05				2	1	2			1	1	1	1				
3 25			1													
3 45						1										
3 65				1	1											
3 85																
4 05																
4 25																
4 45																
4 65																

B lipoprotein values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	2 7	S d x	467	r(x y)	4869	Mean y	93 35	S d y	49 68
Mean log x	347	S d log x	0873	r(log x log y)	5375	Mean log y	1 918	S d log y	2097

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 114 men can be considered as a random sample of the investigated

T bl A III 23 H lth e r ey n th R ykja ik are Stage I 1967 68 M n

Freq y t bl f s rum total chole t rol v lues and serum triglyceride valu s in men

Number of m 118 Ag 34 y ars R sponse 71 6%[1/]

Tot hol mg % / Cl midp	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
	Triglyc rid values in mg/100 ml (mg%) Class midp int minus 0 5 mg % (Class width 20 mg %)															
≤150 5			1													
170 5	2	1	1													
190 5		5	8		2	1	1		1							
210 5		3	2	3	1	2		1								
230 5		5	8	7	2	1	1									
250 5	1	8	3	4	5		3									
270 5		2	2	3	3	3	1		2							
290 5			3	2	1		1									1
310 5			1	2	1											
330 5				1			1		1							
350 5			1	1		1										
370 5					1											
390 5																
410 5																
430 5																
≥450 5																

Total cholest rol values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	244 00	S d x	43 014	r(x y)	2965	Mean y	82 11	S d y	42 11
M an log x	5 482	S d log x	1755	r(log x log y)	3496	Mean log y	4 298	S d log y	4680

1/ % investigated Stag I start d in Nov 67 but the triglyceride measurements began in January 68 B cause of the ppointment system the 118 men can be considered as a random sample of thos inv stigat d

Table A III 28 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum B-lipoprotein values and serum triglyceride values in men

Number of men 19 Age 61 years Response 69 6%[1/]

B lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) ~20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤ 85																
1 05																
1 25			1													
1 45																
1 65																
1 85		1	2	1												
2 05			4	1	1											
2 25			1	4		5										
2 45				1												
2 65																
2 85																
3 05																
3 25																
3 45																
3 65																
3 85																
4 05																
4 25																
4 45																
≥4 65																

B-lipoprotein values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	0	S d x	252	r(x y)	3976	Mean y	74 68	S d y	20 41
Mean log x	306	S d log x	0595	r(log x log y)	3857	Mean log y	1 857	S d log y	1237

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 19 men can be considered as a random sample of those investigated

T bl A III 29 H lth surv y i the R ykjavik re Stag I 1967 68 Men

Freq ncy t bl f s rum total hol st rol alu and erum triglycerid values in men

Number f me 118 Ag 34 y s R spons 71 6%[1/]

T t chole mg %	Triglyc rid alues in mg/100 ml (mg%) Clas midpoint minus 0 5 mg % (Cla s width 20 mg %)															
Cl midp	≤ 20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥ 320
≤ 150 5			1													
170 5	2	1	1													
190 5		5	8		2	1	1		1							
210 5		3	2	3	1	2		1								
230 5		5	8	7	2	1	1									
250 5	1	8	3	4	5		3									
270 5		2	2	3	3	3	1		2							
290 5			3	2	1		1									1
310 5			1	2	1											
330 5				1			1		1							
350 5			1	1		1										
370 5					1											
390 5																
410 5																
430 5																
≥ 450 5																

Total cholest rol values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	244 00	S d x	43 014	r(x y)	2965	Mean y	82 11	S d y	42 11
Mean log x	5 482	S d log x	1755	r(log x log y)	3496	Mean log y	4 298	S d log y	468[illegible]

1/ % investigat d Stag I started in Nov 67 but the triglyceride measurements began in January 68 Becaus of the ppointment system the 118 men can b considered as a random sample of those inv stigated

Table A III 28 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Frequency table of serum B-lipoprotein values and serum triglyceride values in men
Number of men 19 Age 61 years Response 69 6%[1/]

B-lipop mm Immunoc Cl midp	Triglyceride values in mg/100ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %)														
	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
- 85																
1 05																
1 25			1													
1 45																
1 65																
1 85		1	2	1												
2 05			4	1	1											
2 25			1	4		[illegible]										
2 45				1												
2 65																
2 85																
3 05																
3 25																
3 45																
3 65																
3 85																
4 05																
4 25																
4 45																
≥4 65																

B-lipoprotein values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	2 04	S d x	252	r(x y)	3976	Mean y	74 68	S d y	20 41
Mean log x	306	S d log x	0595	r(log x log y)	3957	Mean log y	1 857	S d log y	1237

1/ % investigated Stage I started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 19 men can be considered as a random sample of those investigated

Tll s III 31 ll ltl r y t k ykja k a St g I 1967 68 Men
Freq y t ll f um t t l l l t rol val and s rum t iglyceride valu in men
N be of mo 40 A 40 42 44 y r Re pons 75 4%[1]

Tot hol mg % / Cl midp	Triglycerid values in mg/100ml (mg%) — Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	20
150 5		1		1												
170 5		4	4	3	1											
190 5	3	1	7	10	4	4	2	2	1	1						
210 5		7	9	13	6	4	2		1			1				
230 5	4	9	18	19	17	6	3	3	2	1						
250 5		3	15	15	11	12	6	4	7	4						1
270 5		5	8	20	11	7	5	5	2	4		1				
290 5	1	4	11	5	9	7	3	1	3					1		3
310 5			3	2	3	4	1	3	3						1	
330 5		1	2	2	5	1	1		1							
350 5			1	1	1				1	1				1		
370 5					1			1								
390 5				1												
410 5																
430 5																
450 5					1	1										

Total hol st rol value (x)				Correlation coefficient		Triglyceride values (y)			
n x	251 83	d x	42 956	r(x y)	2552	Mean y	100 20	S d y	50 95
n log x	5 515	S d log x	1679	r(log x log y)	2720	Mean log y	4 495	S d log y	4760

1/ % inv tigated tage I tarted in Nov 67 but the triglyceride measurements began in January 68 B c use of th ppointment system the 407 m n can be consid red as a random sample of th s investigated

Table A III 30 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum total cholesterol values and serum triglyceride values in men

Number of men 121 Age 37 years Response 71 3%[1/]

Tot chole mg %	Triglyceride values in mg/100 ml (mg%)															
Cl midp	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	20	40	60	80	100	120	140	160	180	200	20	240	260	280	300	≥320
< 150 5																
170 5		3	1	1												
190 5		4	4	2												
210 5	1	2	4	3	1	1										
230 5		3	3	8	5	4	3		1	1						
250 5		2	5	2	6		5			1				1	1	
270 5			2	5	2	6	1	1	1						1	
290 5		2	2	4	2		2	4								
310 5		1		1		1	1									
330 5				1			1									
350 5																
370 5									1							
390 5																
410 5				1												
430 5																
450 5																

Total chol sterol values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	248 75	S d x	39 577	r(x y)	3223	Mean y	97 73	S d y	50 72
Mean log x	5 504	S d log x	1576	r(log x log y)	4167	Mean log y	4 465	S d log y	4845

1/ % investigated Stage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 121 men can be considered as a random sample of those investigated

Tal1 n III d1. H lti y th ykj vlk d Stap I 1967 68 Han
Froque y t bl f rum t t l r l t rol v lu a d rum t igly e de alu s in m n
Numb r of a 407 Ag 40 42 44 y rs R pon 75 4%[1/]

T t chol mg % Cl midp	20	40	60	80	100	120	140	160	180	200	2 0	240	260	280	300	* 20
	Trigly do alues in mg/100ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
150 5		1		1												
170 5		4	4	3	1											
190 5	3	1	7	10	4	4	2	2	1	1						
210 5		7	9	13	6	4	2		1			1				
230 5	4	9	18	19	17	6	3	3	2	1						
250 5		3	15	15	11	12	6	4	2	4						1
270 5		5	8	20	11	7	5	5	2	4		1				
290 5	1	4	11	5	9	7	3	1	3					1		3
310 5			3	2	3	4	1	3	3						1	
330 5		1	2	2	5	1	1		1							
350 5			1	1	1				1	1				1		
370 5					1			1								
390 5				1												
410 5																
430 5																
450 5					1	1										

Tot l ch l st rol val es (x)				Correlati n co fficient		Triglycerid values (y)			
Me n x	251 83	S d x	42 956	r(x y)	2552	Mean y	100 20	S d y	50 95
M an log x	5 515	d log x	1679	r(log x log y)	2720	M an log y	4 495	S d log y	4760

1/ % inve tigat d Stage I st rted in Nov 67 but the trigl/ceride measurements began in January 68 Because of the appointment syst m th 407 men can be considered as a random sample of thos investigated

Table A III 30 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum total cholesterol values and serum triglyceride values in men

Number of men 121 Age 37 years Response 71 3%[1/]

Tot cholo mg %	Triglyceride values in mg/100 ml (mg%)															
	Class midpoint minus 0 5 mg %									(Class width 20 mg %)						
Cl midp	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
< 150 5																
170 5		3	1	1												
190 5		4	4	2												
210 5	1	2	4	3	1	1										
230 5		3	3	8	5	4	3		1	1						
250 5		2	5	2	6		5			1				1	1	
270 5			2	5	2	6	1	1	1						1	
290 5		2	2	4	2		2	4								
310 5		1		1		1	1									
330 5				1			1									
350 5																
370 5									1							
390 5																
410 5				1												
430 5																
450 5																

Total chol sterol values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	248 75	S d x	39 577	r(x y)	3223	Mean y	97 73	S d y	50 72
Mean log x	5 504	S d log x	1576	r(log x log y)	4167	Mean log y	4 465	S d log y	4845

1/ % investigated Stage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 121 men can be considered as a random sample of those investigated

T b A III 33 H lth r y the Reykj v k area Stag I 1967 68 Men

Freq ncy t bl of serum total hol st rol v l s and s rum trigly eride values in men

Numbe of m n 392 Ag 50 51 52 54 years Re pon 75 7%[1/]

Tot hol mg % Cl midp	Trigly erid valu s in mg/100 ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %)															
	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
150 5									1							
170 5		1	2	1												
190 5	1	9	5	3	5	1	1									
210 5	1	6	10	7	5	3	2						1			
230 5		8	18	13	6	6	5		1	3	1					
2 0 5	2	8	21	23	7	9	3	1	3	2	5				1	
270 5	1	4	13	13	17	7	4	5	1	1			2			
290 5		1	11	17	1	5	4	3	2		2					
310 5			4	7	5	1	2	2	1	3	1	2				1
330 5		1	6	5	4		1					1		1		
350 5				2	1	1										
370 5							1	1		1						
390 5					1											
410 5				1				1								
430 5																
450 5																

Total chol st rol values (x)		Correlation coefficient		Triglyceride values (y)	
M an x 260 20	S d x 41 790	r(x y)	2319	Mean y : 96 27	S d y : 51 98
M an log x: 5 549	S d log x 1613	r(log x log y)	2666	Mean log y: 4 453	S d log y: 4665

1/ % inv stigated tage I started in Nov 67 but the triglyceride measurements began in January 68 Because of th appointment system the 392 men can be considered as a random sample of those investigated

Table A III 32 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum total cholesterol values and serum triglyceride values in men

Number of men 507 Age 46 47 48 49 years Response 77 3%[1/]

Tot chole mg %	Triglyceride values in mg/100 ml (mg%)															
	Class midpoint minus 0 5 mg % (Class width 20 mg %)															
Cl midp	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤150 5			1													
170 5		1	3	2	2	1										
190 5		5	9	6	1	1			1							
210 5	2	15	15	16	5	3	2		2							
230 5		6	23	21	8	8	5	1	1		2	1				
250 5		11	25	21	20	6	6	5	3	2	1	1	1	1		
270 5	1	8	18	20	14	12	6	6	3			2	1			
290 5		5	7	17	13	7	4	1	4	1	5					2
310 5		2	6	10	8	5	2	1		1	3		1		1	
330 5			3	2	2		2	4	1			1	1		1	
350 5		1	2	1	1	1	1			1						
370 5					1											
390 5				2	1		1	1						1		
410 5					1	1			1							
430 5																
450 5	1								1		1					

Total chol sterol values (x)				Correlation coefficient		Triglyceride values (y)			
Mean x	261 13	S d x	45 520	r(x y)	2872	Mean y	98 59	S d y	53 28
Mean log x	5 551	S d log x	1684	r(log x log y)	2988	Mean log y	4 470	S d log y	4847

1/ % investigated Stage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 507 men can be considered as a random sample of those investiagated

T bl A III 35 He lth ur ey i the R ykjavik area Stage I 1967 68 Men

Freq n y t bl of rum t tal hol t rol al and serum triglycerid value in men

Numbe f m 71 Ag 61 y ar Respon 69 6%[1/]

T t chol mg % Cl midp	Trigly erid valu s in mg/100 ml (mg%) Cla s midpoint minus 0 5 mg % (Class width 20 mg %) ≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤150 5																
170 5			3													
190 5		1	3	2												
210 5			4	2			1									
230 5		2	4	2		4	1	2		1						
250 5		1	2	5	1	1		1		1						
270 5		2		1	1	1										
290 5	1	1	1	4		1	2									
310 5				2	2		1				1	1				
330 5			1	1												
350 5				1												
370 5					1	1										
390 5																
410 5																
430 5																
≥450 5																

Total cholesterol values (x)				Correlation coefficient		Triglyceride values (y)			
M an x	254 76	S d x	46 257	r(x y)	2371	Mean y	92 52	S d y	44 31
M an log x	5 524	S d log x	1805	r(log x log y)	2453	Mean log y	4 426	S d log y	4489

1/ % inv stigated St g I start d in Nov 67 but the triglyc rid measurements began in January 68 Be ause of th appointment system the 71 men can be considered as a random sampl of those investig ted

Table A III 34 Health survey in the Reykjavik area Stage I 1967 - 68 - Men

Frequency table of serum total cholesterol values and serum triglyceride values in men

Number of men 167 Age 56 58 years Response 74 3%[1/]

Tot chole mg % Cl midp	Triglyceride values in mg/100 ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %) 20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	≥320
≤150 5			1				1									
170 5		1		1			1									
190 5		2	2	3												
210 5		4	5	3	4	2	1									
230 5		1	10	3	6	2	2									1
250 5	1	3	8	11	5	2	4		1							
270 5		3	6	11	3	4			1	1						
290 5		1	1	7	5	2	2	1		1						
310 5			4	3	1				2							
330 5			3	3	2	1		1								
350 5				1	1		2				1					
370 5																
390 5			1													
410 5														1		
430 5																
≥450 5																

Total cholesterol values (x)

Mean x 258 99 S d x 44 512
Mean log x 5 542 S d log x 1727

Correlation coefficient

r((x y) 2171
r(log x log y) 2057

Triglyceride values (y)

Mean y 90 86 S d y 42 80
Mean log y 4 423 S d log y 4009

1/ % in estigated tage I started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 167 men can be considered as a random sample of those investigated

T bl A III 26 Health surv y i the R ykja ik area St g I 1967 68 Men
Fr que y t bl of s rum tot l hol t rol valu s and rum triglyc rid valu s in m n
Number of me 71 Ag 61 years R spons 69 6%[1/]

Tot cholo mg %	Triglyceride valu s in mg/100 ml (mg%) Class midpoint minus 0 5 mg % (Class width 20 mg %)															
Cl midp	≤20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	x 20
≤150 5																
170 5			3													
190 5		1	3	2												
210 5			4	2			1									
230 5		2	4	2		4	1	2		1						
250 5		1	2	5	1	1		1		1						
270 5		2		1	1	1										
290 5	1	1	1	4		1	2									
310 5				2	2		1				1	1				
330 5			1	1												
350 5				1												
370 5					1	1										
390 5																
410 5																
430 5																
≥450 5																

Total chol st rol valu s (x)				Correlation coefficient		Triglyc ride values (y)			
M an x	254 76	S d x	46 257	r(x y)	2371	Me n y	92 52	S d y	44 31
Me n log x	5 524	S d log x:	1805	r(log x log y):	2453	Mean log y	4 426	S d log y	4489

1/ % in stigat d Stage I started in Nov 67 but th triglyceride measurements began in Janu ry 68 Beca se of the appointment syst m th 71 men can be consid r d as a random sample of those inve tigated

Tafla A III 36

Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Partial correlation coefficients based on Tables A III 15-35 The correlation coefficients of the untransformed data are used
k = serum β-lipoprotein i = serum total cholesterol j = serum triglycerides

Age in years	$r_{ij\ k}$	$r_{ki\ j}$	$r_{jk\ i}$
34	- 0 342	0 768	0 636
37	- 147	582	610
40 42 44	- 210	632	586
46 47 48 49	- 013	571	401
50 52 54	- 050	606	441
56 58	096	306	327
61	- 083	711	340

DISCUSSION

Method

In a health survey such as the present one it is necessary to employ rapid and convenient methods for ch mical analysis For this purpose an AutoAnalyzer (I) was used which in turn affected somewhat the choice of methods

Beta lipoproteins were quantitated by means of an immuno ch mical method Th method was des ribed by Heiskell et al [16] nd Bergquist et al [17] in 1961

Th advantages of the method are that it is simple and can b rapidly carri d out manually and does not require any ex pensive equipment However reagents are expensive The method is spe ific [16] No quality control was maintained

These assays were not started until May 1968 due to initial difficulties among other things an automated method [18] was first tried out b t thi gave unsatisfactory results

The advantag s of th cholesterol method are that it employs few reagents and is easy to use Apart from the preparation of reag nts and th xtraction which was carried out on the day th blood samples were collected the determination was done on th AutoAnalyz r which saved much time and labour The deter mination of t tal cholesterol nd triglycerides on the same extract mad for greater fficiency Furthermore the method is s n t v and does n t require a larg sampl

Block et al [14] hav publish d a comparison of thi method and th method of Abell et al [19] Th y found all the results f o t rmin t n on serum samples from 60 pati nts to be within 6% f re lts obtained with the method of Abell et al which is red to b both ac urat and precis and is frequ ntly a a ref renc metnod

The method s not very specific sinc various compounds ff t th e ults lo special precautions were taken becau e f nte f r ng factors ch as vitamin A bilirubin polyunsatur-

ated fatty acids and haemolysis [20] [21]

AutoAnalyzer tubing was checked by pinching it between two fingers As soon as it became stiff or flattened it was replaced It is not, however clear how frequently this was done

The precision of the analyses carried out at the clinic can be gauged from the results of the control serum analyses As mentioned on page 25 the standard deviation turned out to be 5 7 mg% corresponding to a coefficient of variation < 3% These results are similar to those of Block et al [14]

It is difficult to state with confidence the accuracy of the analyses The results from the control serum (Table A III 5) show that the mean of the values obtained for Hyland Special Serum over the period from January 31st to May 27th was 13 7 mg% lower than the midpoint value for the stated acceptable range ($p < 0\ 001$) and the mean value obtained for Hyland Normal Serum over the period June 6th to July 4th was 3 4 mg% lower than the midpoint value for the stated acceptable range ($p < 0\ 05$) and for the period from July 9th to September 24th the difference was 8 7 mg% ($p < 0\ 001$) Nyegaards Seronorm being used in this period It should be mentioned that several days or even weeks always elapsed from the time the freeze-dried control serum was dispatched until it was received at the clinic and that the packages were not insulated

The <u>triglyceride method</u> calls for mainly the following comments in addition to what was said in the discussion of the cholesterol method The method is a sensitive one However several compounds interfere with the assay chiefly phospho lipids and glucose The mixture of zeolite $Ca(Oh)_2$ and $CuSO_4$ which was used prevents this interference from phospholipids and from glucose at least up to 250 mg% [13] but higher glucose values are rare

The procedure used deviated from that of Kessler and Lederer [13] in that delay coils were included in the circuit to prevent an unsteady baseline and badly shaped peaks Blanks were not run for individual samples

Analyse were started on January 31st 1968 Control serum was used from January 31st until May 27th 1969 The serum was Hyland Special Clinical Chemistry Control Serum The mean value for 23 assays was 7 9 mg% higher than the midpoint value of the stated ac eptable range This difference is significant (p < 001)

The precision of the analyses is seen from the results of control serum analyses where the standard deviation was 7 4 mg% (p 24)

The control s rum was neither used to evaluate the accuracy of TG measurements nor the accuracy of the cholesterol measurements There is reason to suspect that the long time the control serum spent in transit ffected the results

Seasonal variations

Numerous studies have been published on the variability of the serum lipid levels in the individual Fluctuations during one day and over periods of days weeks months and years have been reported These variations can be consider able depending to some extent on the individual Although these are of great importance they will only be mentioned occasionally in the following discussion on the presence and the extent of seasonal variations in serum lipids levels

The survey was being carried out at full rate from the beginning of December until the middle of July or for 7 1/2 months It is important in relation to the aims of a survey such as this one that the period of the survey covers the greater part of the year When assessing the health benefits from systematic health surveys it may be unsafe to rely on results from surveys completed in a short time e g part of a season Such short-time surveys have indeed been carried out but can give quite erroneous results since for example an epidemic in progress could have unforeseeable effects on the results Furthermore such surveys can not yield valuable information on seasonal variations [1]

It is however not sufficient that a survey such as the present one be spread throughout most of the year It is necessary to ensure that all age groups among the participants are equivalently placed with respect to all conceivable deter mining factors such as time of year and week and appointment time As discussed in Report A II it must be concluded that in this respect the survey was successful [1]

Another factor which may however be unimportant at any rate in this country is the selection of age groups The selection of age groups with say a 5 10 15 years etc age difference may be misguiding since it is conceivable that an epidemic at birth or at a certain age like for example the Spanish flu in 1918 or a periodic epidemic with e g a r 10 year period could affect the health of the surviving mem bers of the age group [1]

Ancel Keys et al ([6] p 22) appear to be of a different opinion in 1966 They state Each area has its peculiarities that affect practical details of organizing and operating cardio v scular surveys and related field work but the following notes are generally applicable to the studies reported here

It is difficult to engage first class professional person nel to stay in the field away from their home headquarters for more than a few weeks at a time so the sched les for field work were planned accordingly Selection of the period for field work in a given area required consideration of the seasonal activity of the subject as well as that of the proposed staff and in gen ral this means concentration of the examinations in a period of not over on month

This does not con titute a erious difference of opinion sinc the difficulties mentioned by Keys et al are either non-existent ir this country or surmountable at any rate as regards Stage I of this health urvey because of a comp terized National Roster a small g ographical rea and th fact that all the work of th survey was in the hands of local residents

The earli st referenc known to us on the seasonal varia-ti n of blood lipid in the Nordic Countri s is a paper by Keys Karvonen and Fidan a (1958) [22] The subject of the p per is a sur y arried out in F nland during 1956 57 The authors mention that in East Finland (Karelia region) th mean valu s for total chol sterol assays during the months of June 56 September 56 and January 57 increa ed from just under 200 mg% to ju t und r 300 mg% or by some 100 mg% both in men and women In We t F nland how er the corresponding increa e is much mall r s me 20 30 mg% The uthors state In the ast the l l ros ignifi antly from June to September but in the La t this s sonal trend was larger and continu d until J nua y when th a r ge w s about 100 mg per 100 ml high r than i Jure Accordingly in comparing s rum-chol sterol l el of p p lati n easonal ariation should b considered t l t regions such a Ea t Finalnd where s sonal diff r-n n limat and mod of life ar extreme It is difficult

for the reader to appraise these statements and the authors do not elaborate these points further

In 1961 J Paloheimo's Monograph Seasonal Variations of Serum Lipids in Healthy Men appeared [23] It reports the first major study conducted solely for the purpose indicated in the title

The study was made on a series of 80 healthy men who volunteered for the study viz 45 policemen (age 25-45 years) employed by the police department of the city of Helsinki (Latitude 60 N) and 35 convicts (age 23-48 years) from the Helsinki Central Prison Initially the total number was 91 but during the course of the study 11 men had to be excluded owing to illness or accident

At monthly intervals in the period Feb 1958 - Jan 1959 fasting blood samples were collected for lipid analysis Only the results of serum total cholesterol determinations will be considered here Cholesterol was determined by the modification of the method of Abell et al [19] introduced by Anderson and Keys (1956) modified by Konttinen (1959)

The error of measurement was estimated by using independent duplications to be s = 4 0 mg% with 39 degrees of freedom It is not mentioned if control sera were used

When testing for seasonal variation the author considered monthly median values rather than monthly mean values and used a model of the type

$$y = \alpha + \lambda \sin \left(\frac{\pi}{6} t + \varphi \right) \qquad (1)$$

where t = 1 (Feb 1958) t = 2 (March) t 12 (January 1959) denotes the average over the period (one year) of the characteristic used (the median) 2λ measure the extent of the seasonal variations since the minimum and maximum value of the function y is α λ and $\alpha + \lambda$ respectively

The function y can also be written in the equivalent rm which was that actually used

$$y = \alpha \quad \rho \sin \frac{\pi}{6} t + \gamma \cos \frac{\pi}{6} t \qquad (2)$$

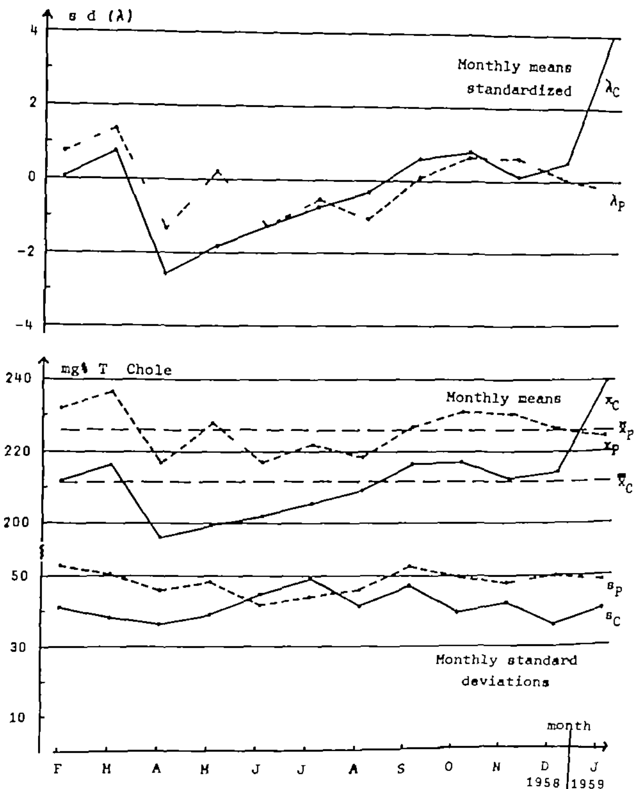
where $\chi^2 = \rho^2 + \gamma^2$ and φ arctg (γ / ρ)

Having done more statistical analysis the author concludes Total cholesterol in the group of policemen showed no seasonal variations although the values were lowest in spring and summer By contrast in the group of convicts total cholesterol fell in ummer and ros in winter and the changes were significant (p 0 025) In this group the minimum value for total cholsterol (median) was observed in May (187 mg per 100 ml) the maximum value in January (232 mg per 100 ml) From the values for F bruary and March the drop to the values for April and May was con iderable In the autumn the values began to rise rea hing the maximum in the middle of th wint r

At the nd of his Di cussion the author writes It ppears ther fore th t it [seasonal variation] i a biologi al phenomenon the sum of many factors which is not strong n ugh to be learly notic abl xcept under conditions where life is extremely regular as it is in prison and where ext rnal infl e ce are light Und r normal conditions such as were p es nt i th group of poli emen the factors influencing the l pid l el are so many and so variabl that the seasonal trend cann t manif st it lf

Th polireren orked by 12 hour shifts but every sixth ay as fr so from this reasor alone it s ems doubtful to s th t th poli emen li ed under normal conditions It hc ld lso b r ntion d that 11 obs (2 6%) were missing from tr nv ts but 48 obs (8 9%) from the p lic ren In the pe od Jun Aug t these number were 2 (1 9%) and 28 (20 8%) r t ly and in J ly they were 1 (2 9%) and 15 (33 3%) sp ti ly

From th curves in Fig 1 in Paloh ino s monograph [2] w i h pr s t 3 month moving a erages o median values we e t mat the e tent of the easonal variation to be about 25 mg% the gro p of on icts and about 10 mg% in the group of police



No of obs pr month Convicts(C) 32 -35 Policemen(P) 30 -44

Figure A III 24 Monthly mean values ($\bar{x}$) monthly standard deviations (s) and monthly mean values standardized ($\lambda = (\bar{x} \quad \bar{\bar{x}})\sqrt{n}/s$)

men When the estimator $2\sqrt{b^2 + c^2}$ is used the estimates become 27 3 mg% and 7 0 mg% respectively

It should be noted that Paloheimo used monthly median values inst ad of mean values This has the advantage of being less sen itive for extreme values due to odd mistakes etc

Fig A III 24 is analogous to our Fig A III 1* p 50 and based on Tabl 10 in Paloheimo s monograph [23] There we considered the monthly mean values after exclusion of one policeman with 3 missing measurements The seasonal variation in the mean values i apparent and seems to be of similar extent as of the median values

W have done a statistical analysis using model (2) The results were

	Regre sion Coefficients			Probability	Residual
	a	b	c	p	s d
Con ict	211 7	6 31	9 0	05	8 8
Policemen	225 8	1 02	4 85	> 1	5 7

H r a b and denot the stimates of the param t rs α β and γ resp ctiv ly

Th e timator $2\sqrt{b^2 \quad c^2}$ of the ext nt of seasonal variation giv 22 1 mg% for the convicts and 9 9 mg% for th policemen The maximum value of th fitted cur s (2) are in Dec and Jan spe tiv ly

By omparing the monthly variance in each group with the riati n of the monthly mean values about the corresponding empiri l curv (fitted curv) it was found that the model fit re nably well

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f run total cholest rol valu s in 35 convicts and 44 policemen
H l inki Finl nd 1958 1959 n no of obs pr month
* gr no mean (B u on Tabl 10 in [23] J Paloheimo)

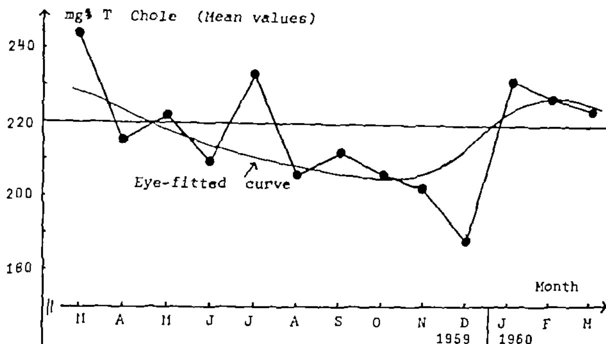


Figure A III 25 From the blood -bank of Bispebjerg Hospital Copenhagen Serum -cholesterol by seasons in 637 blood -donors (men) aged 30 -39 years (Based on Fig 3 in [24] Lund Geill and Andresen)

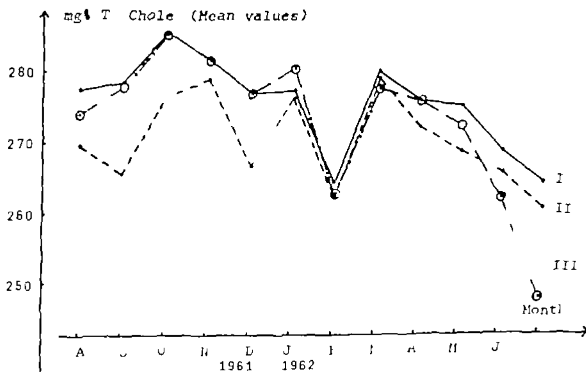


Figure A III 6 The Stockholm Prospective Study I 961 62 Serum -cholesterol concentration in ealthy men in different months I —— age adjusted mean values 1188 men aged 30 64 yrs II - - - age adjusted mean values 1265 men aged 15 74 yrs III —·— mean values non adjusted same 1265 men (Ba ed on Table A 77 in Carlson and Lind tedt

Since the author did not mention the use of control serum the mean value 240 mg% in January 1959 for the group of convicts must be considered suspiciously high as compared with the second highest value 217 mg% found in Oct 1958 The corresponding m dian valu s were 232 mg% and 218 mg% re pectively We have checked that a reasonabl lowering of this value will not affect the statisti al significan e of our test (p = 05)

A paper published in 1961 by E Lund T Geill and P H Andre en [24] deals with total-cholesterol measurements on serum from 2399 blood donors at the Bispebjerg Hospital in Copenhagen (Latitude 56 N) 1757 men and 642 women Blood samples were coll cted from March 19 9 until March 1960 and were all collect ed in the morning Donors were not xpected to be fa ting These authors state the following on seasonal variations Fig 3 hows the seasonal variations in mean cholesterol value for ag group 30 39 years These were exactly the same in the other g groups and there were no distinct fluctuations from month to month Hansen (1954) and Nørgaard (19 6) hav demonstrated a greater prevalence of coronary thrombosis during the winter months on the ba is of ur findings this cannot be a consequence of the erum cholest rol levels being higher during th winter months

Also n this e it is difficult to appraise the authors on lusion They do not mention wh th r control serum was us d or whether th analy es were arried out throughout the period of ll ti n or not It not clear ith r wheth r statistical analys s was don f the phrase no distinct fluctuation from m th to month

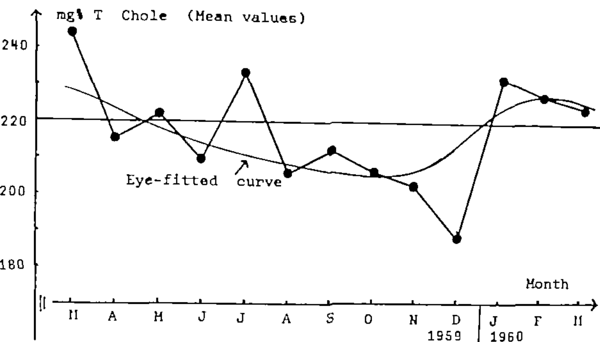


Figure A III 25 From the blood -bank of Bispebjerg Hospital Copenhagen Serum -cholesterol by seasons in 637 blood -donors (men) aged 30 -39 years (Based on Fig 3 in [24] Lund Geill and Andresen)

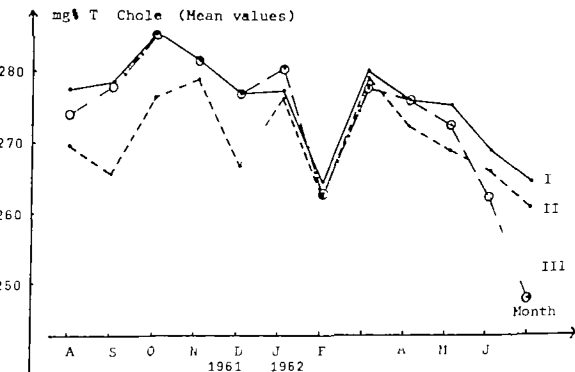


Figure A III 6 The Stockholm Prospective tudy I 1961 62 Serum -cholesterol concertrat on ir ealthy mer n differer ront s I —— age adjusted mean values 1188 men aged 30 64 yrs II - - - age adjusted mean values 1265 men aged 15 74 yrs III —-— r an values non adjusted sare 1 65 men (Based on Table A 77 in Carlson and Lindstedt

for the distribution of the results of cholesterol assays to be similar to that observed in our survey and assuming that each point represents 50 samples then two standard deviations for each point will be 10 - 13 mg% total cholesterol

If the eye fitted curve is valid then the total cholesterol concentration is at a minimum during September-October and at a maximum during February March The extent of this variation will then be some 20 - 30 mg% Only a statistical analysis of the original data can resolve the question of the validity of these conclusions

In 1966 L A Carlson and S Lindstedt published the results of analyses including total cholesterol and triglycerides in the s rum of some 6500 men and women in Stockholm [26]

Samples were collected at Företagens Hälsokontroll - a health control clinic for the employees of several companies - during the period from August 1st 1961 till July 30th 1962 The authors write the following about monthly mean values of total cholesterol in healthy people (group 10) The values for chol sterol followed the same pattern in men and women during the year (T bl s A 77 and A 78) Figure 35 shows that the level was fairly constant from January to May but then declined and reached a minimum level in July The concentration of cholesterol in reased from July to September Octob r and then remained at a rather con tant level The maximal differences in cholesterol l vel during the ye r were 38 and 29 mg per 100 ml for men and women respe tively

Carlson and Lindstedt s curve for men is here shown in Fig A III 25 (C rve III 1 65 men) with the one alteration that the time axis begin in August 1961 when the investigation was tarted instead of January 1962 Curve III could just as well point to sy t matic decrease throughout the period as to a season l variation Perusal of Table A 77 rev als however a diff ren in ge distributions for diff rent months July is pe i lly noticably different with few and predominantly young re Therefore curve II of Fig A III 25 is dr wn after a corre t n of the ag di tribution for each month this corre tion

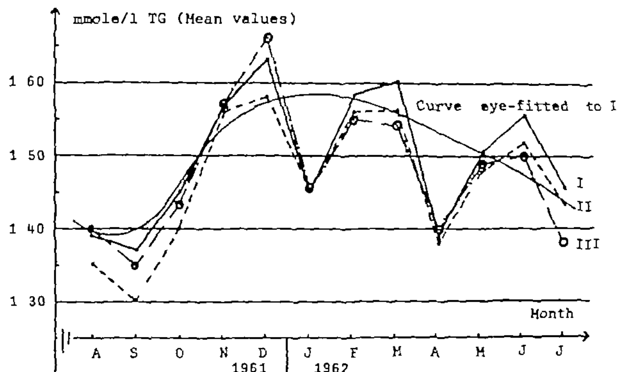


Figure A III 27 The Stockholm Prospective Study I 1961 - 62 Serum triglycerides concentration in healthy men in different months I —— age adjusted mean values 1188 men aged 30-64 yrs II ---- age adjusted mean values 1265 men aged 15-74 yrs III— — mean values non-adjusted same 1265 men (Based on Table A 79 in [25] Carlson and Lindstedt)

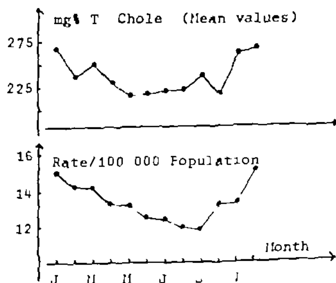


Figure A III 28 Comparison of mean monthly cholesterol levels for 16 prisoners aged 22-28 years with death rates from c rcrary eart disease in the United States in 1958 In the cholesterol graph the value plotted for December was actually obtained on Dec 4 1956 before the other monthly values It has been transposed to the other end to conform to the calender year (Based on Fig 3 r 26 Thomas holljes and Eisenberg)

A graph of average values (Fig 3 Thomas et al) is shown in Fig A III 28 together with a graph of the death rate from coronary heart disease in the USA in 19 8 The results o assays for November 1958 were not used in the preparation of the graph The graph is based on analyses on samples from 16 prison ers Blood samples were collected after breakfast from 9 00 to 11 00 a m There is no mention of a control serum being used The ext nt of the variation appears to be about 50 mg% but it should be noted that the variation for such a small group may deviate markedly from that obtained with a larger sample group

Finally we shall mention a paper by J T Dowle S H Kinch and D F Brown which appeared in 1965 [27] This paper reports a study conducted to determine the presence and extent of seasonal variations in serum total cholesterol concentration in a group of 76 men free of CHD aged 46 62 years The group was selected at random from the Albany Cardiovascular Health Center a prospective study of degen rative cardiovascular disease (Latitude 43 N)

Of the 76 men s lected 69 participated throughout the entire period Of th 69 participants 52 were seen at monthly intervals from April 1961 to March 1962 The data reported are based on these 52

Total cholesterol was measured by the method of Abell et al and th analytical procedure was rigorously controlled The authors state All blood samples were dr wn after an overnight fast and were assayed in duplicate Th specimen tubes were coded so th t all determinations were "blind Duplicate det rminations differing by more than 13 mg/ 100 ml were re analyzed

Coded control sample of known cholesterol concentration were routin ly includ d in all serie of determinations as a check against s ular trend in the analytical proc dure At the completion of the study the ntire y ar s samples for some in di iduals were re analyzed in a single run There were no signi ficant differences in the valu s obtained in the two procedures

Th authors write about their results "The mean group level for April w 227 mg/ 100 ml The study group mean dropped in h of the 3 months to a low of 211 mg/ 100 ml in July The "TCC

being done by weighting the mean cholesterol value in each 5 year cohort in Table A 77" with total number of men in that cohort relative to the grand total number - 1265 Fig A III 26 also shows a curve (Curve I) drawn for the mean values for the age in terval 30-64 similarly corrected for age distributions It is hardly justifiable to conclude from curves I and II that a seasonal variation exists

As to seasonal variation in serum triglyceride levels the situation seems to be different Carlson and Lindstedt state The variation of the triglycerides over the year is given in Figure 36 and Tables A 79 and A 80 The most striking feature was the low level seen in July August and September - for women also in October - which was followed by a pronounced increase to a maximum level in December

Fig A III 27 was drawn after a correction for age like the one carried out for the drawing of Fig A III 26 Two standard deviations for each mean value seem to be about 10 13 mg% From the eye fitted curve the extent of the variation can be esti mated to be about 0 2 mmol/l or about 20 mg% The authors do not state whether a control serum was used

Outside the Nordic countries very few investigations into seasonal variations have been carried out In 1961 C B Thomas H W Holljes and F F Eisenberg [26] report the results of monthly measurements of total cholesterol in the serum of 24 healthy white males ? - 28 years of age all of them prison inmates in Maryland USA (Latitude 39 N) The period of the study was just over a year from the beginning of November 1958 to November 1959 One sample was taken from each inmate each month (with a few exceptions)

The authors make the following statement Highly significant seasonal variations were found with the highest cholesterol values occurring in the winter months and the lowest levels in the late spring summer and early autumn When subjects were grouped according to cholesterol level this cyclic seasonal cholesterol pattern was found to be present in all three groups low inter mediate and high

[serum total cholesterol concentration] then rose steadily until November to 233 mg/ 100 ml In December it dropped to 224 mg/ 100 ml ros in January and February and then began to drop again The mean body weight remained nearly constant over the entire study period Data for the 17 additional persons with incomplete observations are similar

The monthly variation around the mean ranged from 46 mg/ 100 ml in June to 54 mg/ 100 ml in November The monthly distributions of STCC were similar and differ only in the location of the mean

Fig A III 29 shows the monthly mean values and the fitted curve (2) (see p 95) The results of the corresponding analysis were

Regression	Coefficients (mg%)		Probability	R sidual
a	b	c	p	s d
281 3	6 98	3 98	< 0 0005	4 2

Also here we have compared the monthly variance to the variation about the fitted curve and the model (2) seems to fit reasonably well There seems to be no doubt about seasonal variations and a graphical estimate of the extent is about 17 mg% compared to 16 1 mg% when $2\sqrt{b^2 + c^2}$ is used

A weakne s of the model (2) (or (1)) is the assumption that the time interval of increase is equal to the interval of decrease but when we fit a smooth curve by ye (ruling out the possibility of minor peaks [27] [28]) the time int rval of increase was alway considerably shorter than the time interval of decrease and thi also applies to the curves in Fig A III 25 28

The results from the Icelandic Heart Association s Health Surv y do undoubtedly reveal a easonal variation in serum total h l st rol lev ls as seen in Fig A III 14 p 50 (compare the tandard ed d viation (λ) with those of Fig A III 24 p 96) The xtent of the variation during the period December July ppe rs t be 10 mg% but the whol y ar variation will probably be omewhat greater Th levels are highest in March but

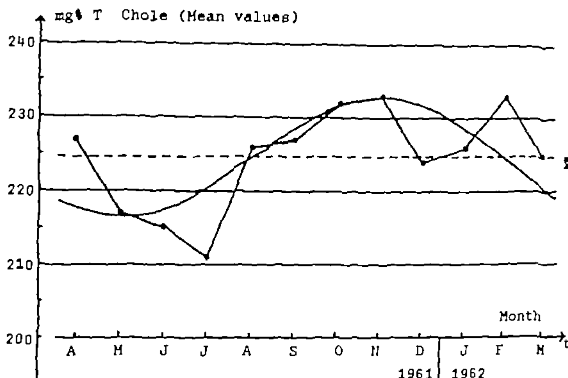


Figure A III 29 From The Albany Cardiovascular Health Center 1961 - 1962 Monthly mean values of serum total cholesterol concentration in 52 healthy men aged 46 - 62 years The least square fitted curve has the equation Y = 224 7 - 6 98sin(30 t) - 3 98cos(30 t) $\bar{X}$= 224 7 mg% = grand mean (Based on Table 1 in [27] J T Doyle et al)

iv) The period of the survey was rather short and the maximum could fall outside this period
v) Carlson and Lindstedt did find a variation by some 0 mg% This need not however be in contradiction to our results since the uncertainty of our assays is somewhat larger and the standard deviation for the distribution of triglyceride concentrations is greater than that for the distribution of total cholesterol values See also paragraph iv
i) The use of control s rum was inadequate (see p 20 26)

As mentioned e rlier no control serum was used for beta lip prot ins and the period in which th se were measured wa hort

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All this serves to illustrate that knowledge of the seasonal variation of various biological param ters is important for epi demiolog l studies and that epidemiologists will necessarily hav to pay more att nt on to them than they have done in the past W thout th knowl dge th comparison of different nations i unreali ti

usually the coldest months are January and February It is interesting to note the absence of any trend (such as a periodic variation) in the weekly standard deviations over this period c f [27]

Arguments supporting the view that the variation is real are

a) All age groups were equivalently placed throughout the survey period ([1] p 21-26) See also bottom line in Tables A III 6 & 12

b) A control serum was run during the period from February 1st to July 4th The results do not suggest any trend neither to decrease nor to increase (Table A III 3 & 4)1/

c) Various physiological effects due to seasonal variations in environmental factors such as temperature - [29]

d) The above mentioned investigations - [22] [23] [26] and [27]

For opposing arguments see the section on triglycerides

Analyses for triglycerides were started in January 1968 The results from the Icelandic Heart Association s Health Survey do not suggest any seasonal variation during the period up to the summer vacation which started in early July (Fig A III 19 p 61)

Arguments supporting the view that there is no seasonal variation over this period are the following

i) See paragraph a) above

ii) A control serum was run from January 31st until May 27th the results of which do not suggest any systematic variatior over this period

The opposing arguments are

iii) One might expect a variation in triglyceride concentration with the variation of some 30 mg% in cholesterol concentra tion On the other hand the correlation coefficient is low (r ≈ 0 25)

1/ See also appendix I and footnote p 27

iv) The period of the survey was rather short and the maximum could fall outside this period

v) Carlson and Lindstedt did find a variation by some 20 mg% This need not however be in contradiction to our results since th uncertainty of our assays is somewhat larger and the standard deviation for the distribution of triglyceride concentrations is greater than that for th distribution of total chole terol values See also paragraph iv

vi) The use of control serum was inadequate (e p 20 26)

As mention d arli r no control serum wa us d for beta lipoproteins and the p riod in which these were measured was short

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All this serve to illu trate that knowl dge of the s asonal v riation of various biological parameters is important for epi demi logi al tudie and that pidemi logists will necessarily have to pay more att ntion to them than th y have done in the pa t Without this knowl dg the comparison of diff rent nations unre listic

Profiles

For each cohort it seems that the results of analyses for beta-lipoproteins on the one hand and total cholesterol on the other are to a reasonable approximation normally distributed i e that conventional models for the statistical analyses of mean values etc are applicable On the other hand the distribution of the results for triglycerides seems clearly skew to the right This is in agreement with the results of other surveys [25] [26] As seen in the fractile diagrams (Fig A III 17 p 59) the results for triglycerides appear to be to an acceptable approximation lognormal in distribution

The coefficients of variation for the distribution of beta-lipoprotein analyses and cholesterol analyses are low (< 0 3) With coefficients of variation as low as this the logarithm will also be normally distributed to an acceptable approximation [31] It has not been checked whether the simultaneous distributions for these two compounds or for all three compounds are normal distributions but the interpretation of the correlation coefficients depends partly on whether this is so or not

Although the results are to an acceptable approximation normally or lognormally distributed one must be cautious to draw on this basis conclusions as to the shape of the tails of the distributions The tails are especially interesting from the medical point of view, since they mainly provide information on abnormal cases

The centile-flow diagrams shown in Figs A III 5 10 and 18 on pages 32 44 and 60 were in part prepared to analyze the tails Curves were drawn through 5% 10% 50% 90% and 95% centiles for the different cohorts in order to reveal how these varied with age For the same reason the fitted curves on pages 32 b 44 b and 60 b were prepared for the above mentioned centiles and for the 30% 70% and 80% centiles too The fitted curves are drawn by eye and therefore subjective

Although these measurements are all done in a short period for all the cohorts it is more interesting although more

risky- to consider the graphs as if they had been prepared after observation of one group of men from the age of 34 to the age of 61 that is over a period of 28 years (hence the term flow dia gram) It is then possible to interpret the centile flow diagrams as follows

The lower fractiles for th b ta-lipoprotein distributions (ay below 50%) are virtually independent of age The highest fractiles (say 90% and higher) seem to be constant up to the age of 50 but then begin to fall off considerably with increasing rate The d crease over the last 10 years of the period is some 0 6 mm IC

All th fractiles for the cholesterol distributions seem to increase up to the age of 50 but after that the lower fractiles and the median values decrease whereas th higher fractiles show a slight increase 0 er the first 15 y ars the higher fractiles increas by s r 20 mg% while the lower fra~tiles increase by som 10 15 mg%

The fractiles in the distributions of the triglyceride re sults are quit int re ting The low and intermediate fractiles how insignificant increases up to the ag of 40 and are constant after that age On the other hand the high fra tiles increase considerably up to the age of 60 this increase being some 25 mg% for the 90% fra tile and some 50 mg% for the 9 % fractil

Considering the composition of beta lipoproteins one might xp t the centil flow diagrams for these to be somewhat inter mediat betwe n tho for chole terol and triglycerides It is nt r t ng th t th centile flow diagrams for the latter two ompoun in some respect quit dissimilar This fact to g ther with the low orrelation coeffici nts suggests that high on ntration of holesterol and triglycerides may be somewhat ndepend nt risk fa tors [4]

De rea e after the ag of 50 in th higher fractiles in the fl w d agrams for the triglycerides could be expl in d by a higher de rat a~o g those with high trigly erid concentrations and/ r by hang s in food onsumption and other habits of life The t v of th lo r and intermediate fr ctiles seems to favour t e former xplanation The same might also explain the f t

that the higher fractiles for the cholesterol distributions do not increase after the age of 45

The flow diagrams appear to support the hypothesis that high total cholesterol concentrations are risk factors for men aged 45 - 49 whereas high concentrations of triglycerides are risk factors for men aged 50 - 54 [4] *Later stages of this survey* may be expected to provide some information on this

It would be interesting to look into the simultaneous effects of these two compounds e g by preparing flow diagrams for the sum of their concentrations and or for the sum of the logarithms of their respective concentrations but this will have to be done later

A discussion of how the consideration of flow diagrams leads to ideas on critical values which appear to be in agreement with the ideas of others is given on p 112

Risk factors and normal values

Some of the reasons for considering high blood lipid concentrations to be risk factors for cardiovascular diseases were mentioned in the introduction

The increased risk of coronary heart disease with increased concentrations of cholesterol has chiefly been demonstrated by prospective studies on large groups of people Among the first of such studies was a study of some 2300 men aged 30 - 62 years in Framingham USA which was begun in 1948 and is not yet completed [32] Included in this group were only men who were found free from CHD on entry The average total cholesterol concentration was found to be about 220 mg% the 95% fractile was about 280 mg% and the 5% fractile was about 160 mg%

For young men (30-49 years old) the risk of CHD turned out to be about 6 times higher for those with serum cholesterol o er 280 mg% than for those with less than 220 mg% [32]

In USA it is generally considered that values over 60 mg

(some say 280 mg%) are abnormal However American studies in dicate that the risk of coronary diseas increases with increas ing cholesterol concentration - also in the low concentration range [3]

The inhabitants of the Karelia region of Finland have among the highest known values for total cholesterol concentration They also have the highest known death rate from coronary heart dis ase (B-26 B 27)1/ In 1961 the death rate was 372 4 per 100 000 for men aged 40 59 years while in the USA the corresponding figure was 365 2 [6]

It is interesting to note that our centile flow diagrams suggest critical values which are in agreement with the figures mentioned above (see Tabl A III 37 p 112)

Examination of the centil flow diagrams for chol sterol concentrations on Figs A III 10 and 10b on pages 44 and 44b reveals that the higher fractiles continue to increase up to the g of 50 but the increas seems to slow down in the age interval 45 49 years and after that it is insignificant Assuming the main reason for the halt in the increase of the fractiles to be that men with high concentration of blood cholesterol tend to die sooner than oth rs then about 270 280 mg% may be said to be ritical value for men aged 45-49 years in that concentrations bov thi value are a serious risk factor

On th other hand th lower fractiles also seem to decrease aft r the age of 50 which an partly be due to th decrease in the high r fractiles but an also be due to other reasons e g chang s in food consumption and oth r living habits However the words of C K Friedberg should be recalled In all th in iden e of ubs quent coronary heart disease was particularly low when th erum chol sterol was b low 200 mg per 100 ml, sug g ting that on ntration abov this valu may be abnormal In most of th studi s th re was a harp ris in the subsequent de v l pment of coronary heart dis ase in groups of individuals with s rum holesterol above 240 or 260 mg p r 100 ml. ([3] p 657)

A similar xamination of th fr tile flow diagrams for

1/ A rding to Tabula codificationis minima

Table A III 37 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Approximate range between the 5%- and the 95% centiles in the distribution of β-lipoprotein values serum total cholesterol values and serum triglycerides values - and suggested critical levels 1/

Age in years	B-lip in mm Immunoc 5%-95% range	crit level	T Chole in mg% 5%-95% range	crit level	TG in mg% 5%-95% range	crit level
35 39	1 4 3 2		180 - 320		40 - 190	
40 49	1 4 3 1	2 5	190 - 330	280	40 - 200	140
50 59	1 4 3 0		190 - 330		40 - 200	

1/ Suggested by the flow-diagrams and explained in text and abstract

triglyceride concentrations (Figs A III 18 and 18b p 60) suggests that the critical value is about 140 mg% for men around the age of 50 The low fractile curves are notably horizontal as compared with the highest fractile ones It is possible that for 2 out of every 3 men the (fasting) triglyceride valu is fairly constant while for the third the value is increased for some reason with the result that by th age of 50 it has become a serious risk factor

Interest in blood triglycerides has been increasing over the last decad The results of various surveys have suggested that high blood concentrations of these may be a risk factor for coro nary h art disease [34]

Albrink [34] is of the opinion that high concentrations of triglyc rides are more common in coronary heart disease than high total cholesterol concentrations and that a triglyceride value of 150 mg% is the value which most clearly distinguishes healthy individuals from c ronary patients Some 80% of the coronary disease patients in her study had blood triglyc ride concentrations in ex s of 150 mg% while only about one third of middle aged men who were considered healthy had these values

Examination of th centile flow diagrams for beta lipoproteins (Figs A III 5 and 5b p 3 and 32b) reveals that the low fractile ur re rtually horiz ntal while the high r fractile urves b g t f ll off c nsid rably after the age of 50 In fact the 95% urv em t b gin to fall off considerably b fore the ag of 50 and th total decreas i about 0 8 mm IC By arguing i the w y as bove one may suggest that the critical value is about 2 5 mm IC It should however be repeated h re that the re s lt are f w in number nd that o qu lity control was maintained

I o v it th aforementioned critical val s atten t t be c w to Fig A III 21 nd 22 on pag s 64 and 65 Here th re ems to be a change in the upward trend of the graph c th mean valu s for th beta lipoprotein results have reached abo t 5 mm IC and the orrespo ding conc ntrations for total le terol nd triglyceride are about 260 mg% and 120 mg% re pecti ly

Table A III 37 Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Approximate range between the 5% and the 95% centiles in the distribution of β-lipoprotein values serum total cholesterol values and serum triglycerides values - and suggested critical levels 1/

Age in years	B-lip in mm Immunoc 5% 95% range	crit level	T Chole in mg% 5%-95% range	crit level	TG in mg% 5%-95% range	crit level
35 39	1 4 3 2	2 5	180 - 320	280	40 - 190	140
40 49	1 4 - 3 1		190 - 330		40 - 200	
50 59	1 4 3 0		190 - 330		40 - 200	

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I co i n with the f ren nti n d critic l valu s atten t r must be drawn to Figs A III 21 and 22 on pag s 64 and 65 Here th re s ems to be a change in the upward trend of the graphs o e th n an alu s for the beta lipoprotein results have reached bout 2 6 mm IC and the corresponding conce trations for total hol t rol and triglyc ride are about 260 mg% and 120 mg% re p ti ly

Table A III 38 Medians of the distributions of serum total cholesterol values of male populations in 7 countries[1/] compared to those of the male population in the Reykjavik area

Age	Finland		Italy			
	Karelia	West -Finl	Crevalcore	Montegiorgio	Nicotera	Rome (Railwaymen)
40 44	265 mg%	248 mg%	194 mg%	192 mg%		207 mg%
45 49	272	255	194 -	192 -	184 mg%	206 -
50 - 54	262	257 -	198 -	199 -	174 -	209 -
55 - 59	259 -	251 -	204 -	198 -	166 -	204 -
Total no of men	814	857	962	710	68	762

Age	Netherlands	Greece	U S A (Railroad employees white)			
	Zutphen	Crete	(Switchmen)	(Sedent clerks)	(Non-sed clerks)	(Executives)
40 44	233 mg%	198 mg%	233 mg%	234 mg%	228 mg%	242 mg%
45 49	235	199	232 -	234 -	230 -	241 -
50 54	227	210	232 -	232 -	255 -	243 -
55 [illegible]	226	208	250 -	242 -	221 -	247 -
Total no of men	831	652	823	853	151	247

Age	Iceland	Japan		Yugoslavia		
	Reykjavik area	Tanushimaru	Ushibuka	Dalmatia	Slavonia	Velika-Krsna
40 44	246 mg%	167 mg%	142 mg%	182 mg%	196 mg%	154 mg%
45 49	253	165 -	143 -	185 -	197 -	157 -
50 54	256	178	137 -	186 -	200 -	159 -
[illegible]	2[illegible]4	168	144 -	188 -	194 -	155 -
[illegible]	817	491	493	666	676	511

1/ [illegible] from [6] A Keys et al

We have discussed centil flow diagrams at some length The reason is not that we valu highly our speculations at this stage but rather that it seems to us that these d agra s should b use ful to epidemiologists and oth rs doing cross ectional studies in the formulation of hypotheses concerning the evolution of most biological values and their potential rol as risk factors Th re is at any rate no doubt that much information is lost wh n only means and standard d viations are consid red as has been common practice until recently The only test of the value of the m thod is experi nce and there should be room for in provement by using a statistical model which would make it po sible to fit the curves more objec iv ly

The con ept of normal alues is commonly us d This con cept its name and us have been s v rely criticiz d for many year Th refore normal value will not b furth r discuss d h re but for refer n a ro gh estimate is gi en of th 5% and 95% fra tiles for th age groups 35 39 40-49 and 0 59 years Th int rval between these estimates i shown in Table A III 37 as 5% 95% rang but co ld more c nveni ntly be called 90% common r ng

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u ff lt e are nc unt d in omparing the re ults of ol te l e s rere t differ t groups f p pl or r fa t can u the groups to be insuffici t y o para l E am s ar a) d fferent thods us d for th s le t o of t pop l t on b) differ nt l v l of parti pat n) d f re t analyt al m thods d) ffe t of s a l ar tions

I rt l s ttemp s na been mad to o e come these iff ulti s An amp e s coordin ted surve s carri d o t in ar co ntr s d ri g the y ar 1957 6 [6] ble A II 38

Table A III 39 Serum total cholesterol mean-values ($\bar{x}$) and standard deviations (s) in apparently healthy men (blood donors) in Norway[1/] and in North Scotland[2/]

Location	Age in years	Number (n)	$\bar{x} \pm 2s/\sqrt{n}$ mg%	s mg%	Method
Trondheim Norway	21- 30	24	192± 15	36	Schoenheimer and Sperry (Fasting blood samples)
	31- 40	30	241± 18	47	
	41- 50	25	243± 18	45	
	51- 60	22	272± 27	61	
	61- 70	9	256± 42	59	
North-Scotland	18- 19	12	187± 9	15	Liebermann-Burchard reaction according to the method of Watson (Samples collected during the winter months)
	20- 24	87	214± 6	30	
	25- 29	99	227± 8	40	
	30- 34	77	249± 10	44	
	35- 39	74	261± 10	42	
	40- 44	78	258± 10	45	
	45- 49	69	271± 11	45	
	50- 54	38	253± 15	45	
	55- 59	32	265± 16	44	
	60 64	21	250± 17	39	
	65- 70	6	243± 32	39	

1/ Based on Table II in [35] (J C Lund et al)

2/ Based on Table IV in [36] (A G Veitch)

page 114 hows the median values of cholesterol results in these countries and in Iceland

On the selection of the population the authors comment as follows The chunk samples dealt with in Europe and Japan though unbiassed in respect to the particular areas selected for study are not claimed to be necessarily good samples of the whole region in which they reside let alone of the countries The U railroad employees studied are not claimed to be an ideal sample of all U S railroad employ es; there were too many men in the samples who refus d to cooperate And the Roman sample may be unrepresentative of railroad mployees in Italy as a whol But we should not d precate too much the samples are better than thos previously studied ([6] p 15)

The participants w re not required to be fasting when the sample was collected Assays were carried out at laboratories in Minnesota and in Naples where they were sent by post in a dried out form on blotting paper The analyses were done accord ing to the method of Anderson and Keys (1956)

Ex eptions to this were as stated by the authors Ex eptions to the practice of making all analyses on dried serum were the Zutphen series in which the analyses of fresh serum were made locally ir addition to the analyses of dried serum in M nne ota and at Tanushimaru and Ushibuka where fresh serum aft r saponification was analysed by the method of colour de- lopment with ferric ion intensification (cf latkis et al 1953 H nl y 1957) A few checks made on dried serum samples ent from Japan to Minn sota indicated only fair agreement o the chol st rol values reported here from the Japanes samples may not be perf ctly comparable with the other s ri s ([6] p 41)

Th great variation b tween nations is interesting The holest rol con entration seems to be greatest among the in habitants of th Karelia region wh re the median value for men aged 40 59 y are is about 260 mg% Running second are the West Finn and th Ic land rs with median values around 250 mg% F ther outh the Italians the Yugoslavs and the Greeks have median val about or le s than 200 mg% It should be mentioned

that the Finnish survey was carried out in the autumn and that the participation was more than 97% Among the Yugoslavs the participation was over 91% and in the rural village of Velika Krsna near Belgrade the perticipation was 96 7% and the median values there were around 160 mg%

Table A III 39 on page 116 shows means and standard deviations for the results of cholesterol measurements in the serum of blood donors in Norway and Northern-Scotland - i e in two neighbouring countries where the inhabitants are considered to be related to the Icelanders

The Norwegian survey was done by J C Lund E Sivertsen and H C Godal [35] Among other things they measured total cholesterol in the serum of 110 clinically healthy men aged 21 - 70 years Of these 101 were blood donors at a Trondheim blood bank

The authors make the following statement about the group "The material presented here cannot with certainty be said to be representative for the population in the city of Trondheim It consists mainly of blood donors and thus is a pre-selected group However self selection within the group has not occurred

Chemical analyses were done on fasting blood according to the method of Sperry & Webb The authors do not state whether a control serum was employed nor in which year or at what time of year the samples were collected

The Scottish study was done by A G Veitch at the Royal Northern Infirmary at Inverness [36] Total cholesterol was measured in the serum af 93 healthy men aged 18 70 years

The author makes the following comment on the methods Samples were collected at the weekly withdrawal sessions during the winter months Total serum cholesterol was estimated useing the Liebermann Burchard reaction according to the method of Watson (1960) A commercially prepared control serum was tested with each batch and the standard deviation obtained wa $\pm$ 8 mg/100 ml%

Comparison of Table A III 39 with the means shown in Table A III 11 on page 43 seems to ndicate that the concentration

of cholesterol among Icelandic men is lower than among cottish men and higher than in Norwegian men As our results on control serum analyses are low compared with the recommend d values as previously mentioned it is possible that the average concentra tion f cholesterol in Icelandic men is a few mg% higher than our results indicate

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Coordinated surveys of triglycerid conc ntrations for many diff rent nations have not been reported Table A III 40 shows th means and standard deviations for the results of triglyceride me surements in the serum of groups of men in Denmark and Swed n

The Swedish survey is that of Carlson and Lindstedt [26] which was mentioned arlier The means in Table A III 40 were al ulated from Table A 79 in [26] for th p riod from Febru ary to Jun 1962

The Danish survey was done in Ålborg by J Dy rberg and N Hjérne [37]

Th s author omm nt as follow on th Ålborg survey 3 3 p r on ged 11-71 s re i c uded in the study Per- tr n t y f d bete mellit s thyroid diseases and c r nary atheros lero is were exclud d Furthermore per ons treat d w th plasma l pid decrea ing drugs were ex luded and so were per ons taking other drugs known to int rf re with lip d metabol sm g drenal steroids and sex hormones

Overwe ght wa d fin d as a weight exceeding the ideal weight 5%

Th examinat or includ s persons with all d grees of physi l ti ity labo atory workers oldi rs lerks phy icians wo kn n hous wi e old age pen ioner and male and female i l Def n member All p rsons were olunteers and none

Table A III 40 Serum triglycerides mean-values ($\bar{x}$) and standard deviations (s) in apparently healthy men in Denmark and Sweden

Location	Age in years	Number (n)	$\bar{x} \pm 2s/\sqrt{n}$ mg%	s mg%	Method
	11- 20	29	78 ± 7	20	
Aalborg[1/]	21- 30	24	98 ± 12	32	Eggstein &
Denmark	31- 40	25	102 ± 19	47	Kreytz (1966)
	41- 50	27	146 ± 27	70	Fasting blood
	51- 60	36	117 ± 18	55	samples collected
	61- 70	21	119 ± 3[illegible]	72	March 1969 to
					Feb 1971
	20- 24	6	88		
	25- 29	20	109		
	30- 34	39	125		
Stockholm[2/]	35- 39	89	127		Carlson (1963)
Sweden	40- 44	121	139		Fasting blood
	45- 49	103	147		samples collected
	50- 54	93	130		Feb to June
	55- 59	55	130		in 1962
	60- 64	24	122		
	65- 69	10	127		

1/ Based on Table V in [37] (J Dyerberg et al)
2/ Based on Table A 79 in [25] (L A Carlson et al)

were hospital patients [37]

Altogether 194 men participated but in Table A III 40 32 of th se are excluded due to overweight

Chemical analyses were done on fasting blood using the method of Eggstein and Kreutz (1966) The analytical error for individual analys s was estimated by duplicate measurements as being 6 mg% Control serum was used Du to possible seasonal variations the participants were distributed equally over the period of the survey from March 1969 to February 1971

Comparison of the means obtained in these two surv ys with thos obtained in the pres nt reveals a much lower level of triglycerides among the Icelanders E n though the samples con erned are not completely comparable this large differenc in the mean values (about 10-30 mg%) must be quite unexpected As mentioned earlier the employment of the control serum in the triglyc ride as ays during this first stage of the survey was inad quate but the results obtained do not ugg st that our mean values are too low

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In later years a few survey have been carried out which in lud d measurements of blood beta lipoproteins As we are howe r not aware of any su h survey employing an analytical method which we con ider comparable to the one used in this sur y no comparison with other surveys is made here

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Table A III 40 Serum triglycerides mean-values ($\bar{x}$) and standard deviations (s) in apparently healthy men in Denmark and Sweden

Location	Age in years	Number (n)	$x \pm 2s/\sqrt{n}$ mg%	s mg%	Method
Aalborg[1/] Denmark	11- 20	29	78 ± 7	20	Eggstein & Kreytz (1966) Fasting blood samples collected March 1969 to Feb 1971
	21- 30	24	98 ± 12	32	
	31- 40	25	102 ± 19	47	
	41- 50	27	146 ± 27	70	
	51- 60	36	117 ± 18	55	
	61- 70	21	119 ± 32	72	
Stockholm[2/] Sweden	20- 24	6	88		Carlson (1963) Fasting blood samples collected Feb to June in 1962
	25- 29	20	109		
	30- 34	39	125		
	35- 39	89	127		
	40- 44	121	139		
	45- 49	103	147		
	50- 54	93	130		
	55- 59	55	130		
	60- 64	24	122		
	65- 69	10	127		

1/ Based on Table V in [37] (J Dyerberg et al)

2/ Based on Table A 79 in [25] (L A Carlson et al)

The fractile flowdiagrams provided an opportunity for a short discussion of blood lipids as risk factors for coronary heart disease in the dis ussion In the introduction a f w oth r risk fa tors were mentioned which will not be discussed here Coronary diseases are a part of a larger group of diseases termed cardiovascular diseases Table A III 41 shows the pro bability for a few different nations that a forty year old man will die of a cardiovascular disease before the age of fifty and sixty These probabilities are estimated on the basis of figures from 1964 in [39] (S H Preston N Keyfitz and P Scho n)

Table A III 42 shows the probabilities that a forty year old Icelandic man will die of the most common causes of death before h reaches the ages of fifty sixty and seventy respectiv ly

The table shows that c rdiovascular diseases are the most common caus of death for Icelandic males in their prime These probabilities are stimated on the basis of figures from 1964 ([39] Pre ton et al)

Table A III 41 Estimated probabilities that a 40 year old man in a specified country will die from cardiovascular disease[1/] within 10 and 20 years The estimates are based on the 1964 mortality statistics[2/]

Country	The probability that a 40 year old man will die from cardiovascular disease before reaching the age of Fifty	Sixty
Finland	3 15 %	10 97 %
United States	2 59 -	8 70 -
Scotland	2 44 -	9 41 -
England and Wales	1 77 -	7 16 -
Iceland	1 50 -	5 68 -
Denmark	1 18 %	5 61 %
Germany(Fed Repub)	1 33 -	5 58 -
Italy	1 33 -	5 14 -
Norway	1 00 -	4 78 -
Netherlands	1 22 -	4 76 -
Sweden	o 94 %	4 50 %
Yugoslavia	o 85 -	3 87 -
Greece	o 74 -	2 97 -

1/ Comprises B22 24-29 and A85 - 86 in the Sixth and Seventh Revisions of the International Classification (1948 1955)

2/ The estimates are based on figures in [38] (Preston et al)

[8] Meteorological Bureau of Icel Veðráttan
Veðurstofa Íslands 1931 - 70 Reykjavík

[9] J St ff ns n The Physical anthropology of the Vikings
J Royal Anthropol Inst Great Brit & Ir
Vol 83 1953

[10] A Brekkan Blóðf okkar 3862 íslenzkra kvenna
Læknabl Vol 38 138 144 1954

[11] B Thorst insson: Enska öldin
Mal og menning Reykjavík 1970

[12] Stat Bureau of Ic l Population census and vital statistics
Hagstofa Ísland 1903 63 Reykjavík

[13] G Kessler and H Lederer Fluorometry Measurements of Trigly rides
Automation in Analytical Chemistry
Technicon symposia New York
Medical Inc 1965

[14] W L Block K J Jarrett and J B Levine An Improved A tomat d D terminati n of S rum Total Cholest rol with ingle Color g nt
Clin Chem 10 681 689 1966

[15] Le a d B Zak Automated determinati n of erum total chol terol
Clin Chim Acta 10 p 381 384 1964

[16] C L H i k ll P T Fisk W H Fl rsheim A T chi J R Good an and C H Carpent r A simple m thod for quantitation f rum bet lipoprot ins by m ans of the immunocrit
Am J Clin Pathol 3 3 222 1961

[17] L M Be gq ist V P Caroll and R L S arcy Evaluation of pe ific nti rum f r serum- β lip protein sti at o s
Lanc t 1: 537 1961

Table A III 42 Estimated probabilities that a 40 year old man will die from specified causes within next 10 20 and 30 years The estimates are based on the 1964 mortality statistics[1/]

Causes[2/]	Probability that a 40 year old Icelandic man will die before reaching the age of		
	Fifty	Sixty	Seventy
Respiratory T B B 1	o 0 %	o 0 %	o 0 %
Other infec and paras. B 2-17	o 0 -	o 0 -	o 0 -
Neoplasms B 18-19	o 5 -	3 7 -	9 5 -
Cardiovascular B 22 24-29 A 85-86	1 5 -	5 7 -	13 7 -
Infl Pneu bronch B 30-32	o 2 -	o 4 -	o 8 -
Diarrheal B 36	o 0 -	o 0 -	o 0 -
Certain degenerative B 20 33 37-38	o 3 -	o 4 -	1 1
Motor vehicle BE 47	o 1 -	o 2 -	o 6 -
Other violence Be 48-50	1 25-	2 4 -	3 6
Other and unknown	o 4 -	1 0 -	2 9 -
All causes	4 22	13 92 %	32 25 %

1/ The estimates are based on figures in [38] (Preston et al)

2/ According to the International Classification - the Sixth and Seventh Revisions (1948 1955)

ABSTRACT

This report presents the results of s rum β lipoprotein total cholesterol and triglycerides d terminations in a male population surveyed 1967 68

This was th first stage (stage I) in a prosp ctive health survey c nducted by the I elandic H art Association The area of study was th city of Reykjavík with adjacent suburbs and communes The population invit d was 1/3 of each of 16 year groups of males in the age int rval 34 61 y ars The population was s lected from the National Roster according to birthdays i e the 1st 4th 7th of each month the total number being 2 955 The respon e was 75 1%

B lipoproteins were determined with the Hyland Beta L Test total chole terol and triglycerides on Te hnicon AutoAnalyzer (I) according to Technicon Methodology N-24a and a modification of the method of Kessler and Lederer respe tively

Control sera were run in conn ction with chol sterol and triglycerides d terminations

Serum chole terol l vel w re similar to the highest report d from other ountri s ntrary to th triglycerides level which are in tn low range

Th mean val s and lower centil s are practically independ ent of g wh re th higher entil are markedly age-de p nd nt

A n l variation for th chol sterol weekly mean values w f und Th val were highest in winter and lowe t in umme th diff ren timated to b 30 40 mg% No s as nal ar on of tr glyc rid was f und

nt l flowdi grams for these blood lipids are presented and t u of similar flowdi grams is sugg sted a an aid to br dg a gap betw en the interpretation of cross ectional and long tud nal studie

REFERENCES

[1] O J Björnsson D Davíðsson Ó Ólafsson N Sigfusson og Th Thorsteinsson Report A II
Health survey in the Reykjavik area Stage I 1967 - 68 Participants invitations response etc
Heart Preventive Clinic Reykjavik 1972

[2] D S Fredrickson R I Levy and R S Lees Fat transport in lipoproteins An integrated approach to mechanisms and disorders
New Eng J of Med 276 34 94 148 215 273 1967

[3] *L A Carlsson Serum lipids in men with myocardial infarction*
Acta Med Scand 167, 399 1960

[4] M J Albrink Serum lipids hypertension and coronary heart disease
Amer J Med 31 4 1961

[5] A Keys Concluding remarks p 399 - 405 in Atherosclerosis Proceedings of the Second International Symposium Ed R J Joens
Springer Verlag Berlin 1970

[6] *A Keys C Aravanis H W Blackburn* F P van Buchem F Buzina B S Djordjevic A S Dontas F Fidan a M J Karavoren N Kimura D Lekos M Monti V Puddu H L Taylor
Epidemiological studies related to coronary heart disease Characteristics of men aged 40-59 in seven countries
Acta Med Scand Supplementum 460
Finland 1966

[7] D Davíðsson Ahrif þorskalysisinngjafar a kolesterol i blóðvatni
Unpublished

[8] Meteorological Bureau of Icel Veðrattan
Veðurstofa Íslands 1931 70 Reykjavík

[9] J Steffensen The Physical anthropology of the Vikings
J Royal Anthropol Inst Great Brit & Ir
Vol 83 1953

[10] A Brekkan Bló flokkar 3962 íslenzkra kvenna
Læknabl Vol 38 138 144 1954

[11] B Thorsteinsson En ka öldin
Mál og r nning Peykjavík 1970

[12] Stat Bureau of Icel Population census and vital statistics
Hagstofa Íslands 1903 63 Peykjavík

[13] G Ke ler and H Led r r Flu ror try Measurements of
Trigly erid
Automati n in Analytical Chemistry
Techni on Symposia New York
Medical In 1965

[14] W L Block K J Jarrett and J B Levine An Improved
A tomated Determination of Serum Total Chole terol
w th ingl Color P agent
Clir Chem. 10 681 689 1966

[15] J Le ne nd B Zak Automated determination of serum total
hole terol
Clin Chim Acta 10 p 381 384 1964

[16] C L H k ll P T F sk W H Florsheim A Tachi J P
Jordman and C H Carpenter A simple r thod for quantitation
of ur beta lipoproteins by means of the immunocrit
Am J Clin Pathol 35 3 222 1961

[17] I Be gq ist V P Caroll and P L Searcy Evaluation
f pe ific antis rum for serum J lipoprotein sti
mat e
Marc t 1 537 1961

[18] J Kahan and L Sundblad Automated Immunochemical Determination of B-lipoproteins
Automation in Analytical Chemistry
Technicon Symposia 1966 Vol II
New York 1967

[19] L L Abell B B Levy B B Brodie and F E Kendall
A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity
J biol Chem 195 357 1952

[20] R J Henry Clinical Chemistry
Harper and Row N Y 1964

[21] A Del Vecchio Cholesterol Determination by the Zlatkis Method
Lancet 1 1298 1960

[22] A Keys M J Karvonen and F Fidanza Serum-Cholesterol Studies in Finland
Lancet 2 175 1958

[23] J Paloheimo *Seasonal variations of serum lipids in* healthy men
Ann Med Exp et Biol Fenniae 39 Suppl 8 1961

[24] E Lund T Geill and F H Andresen Serum-Cholesterol in *Normal Subjects In Denmark*
Lancet 2 1383 1961

[25] L A Carlson and S Lindstedt The Stockholm Prospective Study I *The Initial Values for Plasma Lipids*
Acta Med Scand Suppl 493 1968

[26] C B Thomas H W D Holljes and F F Eisenberg
Observations on seasonal variations in total serum cholesterol level among healthy young prisoners
Ann Int Med 54 413 1961

[27] J T Doyle S H Kinch and D F Brown Seasonal variation in erum cholesterol concentration
J chron Dis 18 657 1965

[28] J M Thorp Effects of seasonal variation on lipid meta bolism in animals and man
In The Control of Lipid Metabolism
(Biochem Soc Symp No 24 d J K Grant)
Academic Press London 1963

[29] A C Burton and O G Edholm Man in a Cold Environment
Edward Arnold Ltd London 1955

[30] A Keys O Mickelsen E V Miller E R Hayes and R L Todd The concentration of chole terol in the blood serum of normal man and its relation to age
J clin Inv t 29 1347 1950

[31] A Hald Statistical Th ory with Engineering Applications
John Wiley & Sons Inc N Y 1957

[32] W B Kannel M J Schwartz and P M McNamara Blood Pressure and Ri k of Coronary Heart Disease
The Framingham Study
Dis Chest 56 43 1969

[33] C K Fr edberg Dis as s of the H art p 656 p 657
W B Saund rs Co Philad lphia 1967

[34] M J Albr nk Trigly erid s Lipoproteins and Coronary Art ry Di ea
Arch Int rn Med 109 145 1962

[35] J C Lund E i rt sen and H C Godal tudies on S rum Lipids I H althy Indi iduals
Acta M d Scand 169 623 1961

[36] A V t h A urv y of Serum Cholesterol Levels in Appar e tly H althy Individual in the North of Scotland
Health Bulletin 28 56 1970

[37] J Dyerberg and N Hjórne Plasma lipid and lipoprotein levels in a Danish population
Acta Med Scand 191 413, 1972

[38] S H Preston N Keyfitz and R Schoen Causes of Death Life tables for national populations
Seminar Press Inc N Y 1972

A P P E N D I X

T bl A III, 43 | ltl s ey i the l ykj k re t g I 1967 68 ll n
Ag or cifi corrol t ffi ents of the di t ib ti ns of rum β lip protein v lu s (ms Immunocrit
total hol st rol 1 (mg%) no t glyc rid s alu (mg%) n m n Total respo se 75 1%[1/]

Ag in	β lip p x	7	thole t rol	b lipop	T iglyce ide z		T Ch l sterol y		Triglyc rides
y r	No	r(x y)	r(l gx l gy)	lo	r(x z)	(logx logz)	No	r(y z)	r(logy logz)
61	19	7282	7962	19	1 76	3857	71	2 71	249
9	16	4541	794	15	7753	6862	70	1 76	58
56	27	1913	789	27	2426	2417	97	65	66
54	3	6959	6886	33	42 3	5 75	1 4		7
52	27	9935	61	27	416	5127		20 7	1
51	2	6096	5891	29	6534	7 25	0	1187	1432
50	2	4170	5590	25	4155	4172	91	260	2
49	23	3912	441	23	6795	6136	100	6	41
48	52	4992	5560	51	6202	5480	14	77	1
47	46	9412	7770	46	2945	3045	146	51	27
46	4	4747	5907	33	5039	4531	121	66	27
44	51	756	6 65	51	9139	99	1	4	2 1
42	47	5620	5911	47	682	6454	3	2	
40	48	6029	6 0	48	6045	5752	135	1 1	2 9
37	3	6278	6298	34	6514	6619	1	2	4167
34	33	7589	7734	33	6207	586			4

1 % invo tig t d The first stage (t ge I) start d in No 1967 but th triglycerid s measurements began in J nuary 1968 nd th β lipoprot in measurem nts beg n n M y 1968

Table A III 44 health survey in the Reykjavik area Stage I 1967 - 68 - Men

Deciles of the distributions of serum β-lipoprotein values in men Total response 75 1%[1/]

birth year	Age in years	No of meas	Deciles[2/] in mg% 10%	20%	30%	40%	50%	60%	70%	80%	90%
1907	61	19	18	19	20	20	21	22	22	23	23
1910	58	16	16	18	20	21	23	25	28	29	38
12	56	27	18	19	20	21	21	22	23	24	26
1914	54	33	17	18	20	20	21	24	25	25	28
16	52	27	18	19	20	20	21	21	24	28	29
17	51	29	18	19	20	21	23	24	25	30	31
18	50	27	18	19	20	21	22	24	25	29	31
1919	49	23	16	17	18	20	21	22	24	26	29
20	48	52	18	20	21	21	23	26	29	30	31
21	47	46	16	18	19	20	21	21	24	28	32
22	46	40	17	20	21	22	23	23	24	26	30
1924	44	51	18	19	20	21	22	23	24	27	30
26	42	47	18	19	20	21	22	23	24	25	29
28	40	48	17	18	20	22	23	23	25	28	31
1931	37	38	16	18	20	22	23	24	25	30	34
1934	34	33	18	18	19	20	21	23	25	28	29

1/ % investigated The first stage (Stage I) started in Nov 1967 but the β-lipoprotein measurements began in May 1968 Because of the appointment system the 556 men can be considered as a stratified random sample f those investigated

2/ Cutting points below which are found 10 20 30 etc percent of the values

Table A III, 45 h lth surv y in th Reykj ik area St ge I 1967 68 M n Total response 75 1[1/]

f ic l char cteri tic of the di tributions of β lipoprotein alues in men

Birth y ar	Age i y ars	No of m as N	M s % of no exam	β-lipoprot ins in mm Immunocrit: M an $\bar{x}$	s d s	$s/\sqrt{N}$	Min $x_{(1)}$	Max $x_{(N)}$	Range $x_{(N)}$ $x_{(1)}$	2nd mom m_2	b_1	b_2 [2/]
1907	61	19	63 3	2 04	25	06	1 30	2 40	1 10	06	-1 17	4 96
1910	58	16	51 6	2 40	70	17	1 30	3 80	2 50	46	66	2 85
12	56	27	61 3	2 15	35	07	1 50	3 30	1 80	12	1 12	5 72
1914	54	33	73 3	2 23	46	08	1 40	3 60	2 20	21	74	3 81
16	52	27	56 2	2 19	44	08	1 40	3 00	1 60	18	39	2 25
17	51	29	69 0	2 37	52	10	1 60	3 60	2 00	26	65	2 68
18	50	27	65 8	2 40	76	15	1 70	5 50	3 80	55	2 63	11 36
1919	49	23	57 5	2 20	57	12	1 50	4 00	2 50	31	1 44	5 34
20	48	52	65 8	2 42	61	08	90	3 80	2 90	36	17	2 77
21	47	46	65 7	2 27	76	11	80	5 00	4 20	56	1 38	5 67
22	46	40	66 6	2 30	60	09	1 50	5 00	3 50	35	2 25	11 67
1924	44	51	69 8	2 26	55	08	1 20	4 40	3 20	30	1 21	5 94
26	42	47	72 2	2 29	55	08	1 60	4 50	2 90	30	1 88	7 41
28	40	48	65 7	2 32	56	08	1 50	4 20	2 70	30	1 09	4 43
1931	37	38	67 8	2 39	68	11	1 10	4 20	3 10	46	69	3 32
1934	34	33	68.7	2 22	53	09	90	3 40	2 50	28	10	2 97
Total		556	65 7	2 29	58	02	80	5 50	4 70	33	1 35	6 75

1/ % investigated (examined) The first stage (Stage I) started in Nov 1967 but the β lipoprotein measurement began in May 1968 Because of the appointment system the 556 men can be considered as a stratified random sample of thos investigated

2/ m_2 $(1 \quad 1/N)s^2$ b_1 $m_3/m_2^{3/2}$; b_2 m_4/m_2^2

Table A III 46 health survey in the Reykjavík area Stage I 1967 - 68 - Men

Deciles of the distributions of serum total cholesterol values in men Total response 75 1%[1/]

Birth year	Age in years	No of meas	Deciles [2/] in mg/100ml (mg%) 10%	20%	30%	40%	50%	60%	70%	80%	90%
1907	61	87	196 2	219 3	232 0	238 2	246 6	259 2	281 4	290 1	313 8
1910	58	85	195 5	224 9	235 5	244 7	253 0	264 5	275 5	291 9	325 5
12	56	126	202 7	215 1	230 3	246 7	254 5	261 1	273 4	285 8	309 6
1914	54	127	205 8	219 9	231 9	248 8	256 6	267 9	278 3	295 6	313 8
16	52	126	194 5	213 6	227 6	240 8	251 1	259 0	269 0	286 1	307 3
17	51	125	211 2	227 2	237 3	249 4	257 3	265 9	276 4	292 2	308 8
18	50	117	199 0	221 5	240 6	248 9	257 3	267 0	281 3	291 3	313 5
1919	49	127	206 7	223 6	236 9	246 6	257 0	268 9	277 8	286 2	303 8
20	48	175	207 5	222 8	233 9	242 0	250 8	263 0	275 8	287 6	305 5
21	47	172	203 0	212 8	222 5	234 8	245 5	259 7	271 6	285 2	307 5
22	46	149	206 6	224 9	238 4	251 2	257 7	269 8	283 6	300 8	318 8
1924	44	165	197 3	213 8	223 8	233 5	246 4	256 8	268 6	279 8	297 4
26	42	163	192 6	216 1	226 8	236 3	245 8	259 2	271 6	288 7	310 1
28	40	160	199 3	214 5	225 2	235 2	245 5	255 2	265 5	280 5	298 5
1931	37	149	191 8	211 2	223 6	234 0	244 1	255 2	263 0	277 9	294 9
1934	34	141	190 6	200 0	217 8	231 3	239 1	248 8	258 9	275 8	296 8

1/ % investigated

2/ Cutting points below which are found 10 20 30 etc per cent of the values

Table A III 47 H lth surv y in the Reykja ik area Stage I 1967 68 M n
Numerical char cteristic of th distributions of cholesterol v lu in men Total response 75 1%[1/]

Birth year	Ag in y ars	No of meas N	N as % of no exam	Serum total cholesterol in mg% Mean $\bar{x}$	s d s	$s/\sqrt{N}$	Min $x_{(1)}$	Max $x_{(N)}$	Range $x_{(N)}$ $x_{(1)}$	2nd mom m_2	b_1	b_2 [2/]
1907	61	87	100 0	255 18	45 37	4 86	168 00	380 00	212 00	2034 86	42	2 94
1910	58	85	98 8	257 02	44 26	4 80	156 00	355 00	199 00	1936 33	15	2 84
12	56	126	98 4	255 78	43 95	3 92	158 00	401 00	243 00	1916 59	56	3 64
1914	54	127	100 0	259 28	41 53	3 69	182 00	375 00	193 00	1711 05	29	2 55
16	52	126	99 2	249 52	41 30	3 68	143 00	336 00	193 00	1692 47	- 15	2 73
17	51	125	100 0	258 92	41 75	3 73	136 00	414 00	278 00	1728 75	27	4 23
18	50	117	100 0	260 56	46 13	4 26	172 00	420 00	248 00	2110 01	60	3 92
1919	49	127	100 0	258 66	41 03	3 64	172 00	402 00	230 00	1669 86	73	4 50
20	48	175	100 0	256 33	45 07	3 41	161 00	512 00	351 00	2019 39	1 40	9 36
21	47	172	99 4	252 67	45 84	3 50	166 00	452 00	286 00	2088 98	1 14	5 44
22	46	149	99 3	264 44	47 17	3 86	158 00	420 00	262 00	2210 52	59	3 54
1924	44	165	98 7	248 99	41 65	3 24	169 00	460 00	291 00	1724 39	96	5 92
26	42	163	99 4	251 54	46 71	3 66	158 00	450 00	292 00	2168 32	62	4 25
28	40	160	100 0	249 04	40 05	3 17	171 00	392 00	221 00	1594 24	67	3 67
1931	37	149	100 0	246 19	41 39	3 39	156 00	416 00	260 00	1701 90	72	4 62
1934	34	141	100 0	241 99	43 20	3 64	144 00	378 00	234 00	1852 89	47	3 27
Total		2194	99 6	253 78	43 83	94	136 00	512 00	376 00	1920 12	66	4 49

1/ % investigated (examined) 2/ m_2 $(1 - 1/N)s^2$; b_1 $m_3/m_2^{3/2}$; $b_2 = m_4/m_2^2$

Table A III 48 Health survey in the Reykjavík area Stage I 1967- 68 - Men

Deciles of the distributions of serum triglyceride values in men Total response 75 1% 1/

Birth-year	Age in years	No of meas	Deciles 2/ in mg /100ml (mg%) 10%	20%	30%	40%	50%	60%	70%	80%	90%
1907	61	71	47 9	57 4	65 3	72 9	80 0	87 1	105 3	125 0	150 1
1910	58	70	48 0	56 8	64 2	71 6	78 9	86 3	96 0	108 7	140 5
12	56	97	52 0	60 9	69 7	77 0	84 2	92 0	104 1	119 7	142 8
1914	54	105	42 9	53 4	60 9	68 4	79 3	91 9	106 9	123 8	149 1
16	52	96	45 7	59 0	70 3	77 0	83 6	90 2	105 8	129 9	184 5
17	51	100	53 5	60 9	68 3	75 5	82 6	89 8	100 5	113 0	145 5
18	50	91	47 9	59 6	69 7	79 8	89 9	100 6	112 8	141 4	180 0
1919	49	100	43 0	54 7	65 2	74 7	83 0	91 8	105 2	123 8	165 5
20	48	140	51 1	59 9	68 6	78 4	88 4	100 1	114 5	140 5	180 5
21	47	147	43 9	55 4	64 1	72 9	82 1	91 8	107 2	128 3	165 6
22	46	122	53 6	62 6	71 4	78 6	85 8	94 7	106 9	122 8	162 5
1924	44	140	45 5	58 6	69 0	80 5	92 1	103 3	116 8	137 2	170 5
26	42	134	46 8	59 5	70 6	77 7	84 7	93 0	107 1	125 1	166 5
28	40	135	53 0	62 6	72 2	81 2	90 2	100 5	111 1	128 0	160 5
1931	37	121	43 6	56 4	67 9	77 2	85 9	97 5	113 3	133 3	154 1
1934	34	118	37 8	47 7	56 1	64 0	72 2	82 5	93 8	108 5	136 0

1/ % investigated The first stage started in Nov 67 but the triglyceride measurements began in January 68 Because of the appointment system the 1787 men can be considered as a stratified random sample of those investigated

2/ Cutting points below which are found 10 20 30 etc per cent of the values

_abl A III 49 I lth y l th Reykj vik re St g I 1967 68 M n Total respons 75 1%[1]
lure i l cha t ti f th di trib tio s of triglycerides value in men

Birth ye	Ag i y rs	I f no N	M a % of no xam	Serum triglycerides in mg% Mean x̄	s d s	s/√N	Mi $x_{(1)}$	Max $x_{(N)}$	Range $x_{(N)}$ $x_{(1)}$	2nd mom m_2	b_1	b_2 [2]
1907	61	71	81 6	92 52	44 31	5 26	28 00	238 00	210 00	1935 69	1 31	4 61
1910	58	70	81 4	88 30	45 72	5 46	33 00	337 00	304 00	2060 01	2 77	14 29
12	56	97	75 7	92 71	40 71	4 13	30 00	282 00	252 00	1640 47	1 72	7 31
1914	54	105	82 6	90 90	44 81	4 37	35 00	295 00	260 00	1988 77	1 59	6 70
16	52	96	75 6	97 94	52 83	5 39	18 00	280 00	262 00	2762 39	1 42	4 75
17	51	100	80 0	93 13	43 46	4 35	48 00	268 00	220 00	1869 83	1 92	6 82
18	50	91	77 7	104 13	65 46	6 86	25 00	510 00	485 00	4238 53	3 01	17 76
1919	49	100	78 7	95 81	55 49	5 55	35 00	355 00	320 00	3048 55	1 94	7 88
20	48	140	80 0	105 78	61 81	5 22	10 00	450 00	440 00	3792 72	2 15	9 98
21	47	147	84 9	95 56	50 87	4 20	22 00	281 00	259 00	2569 72	1 38	4 79
22	46	122	81 3	96 84	42 30	3 83	32 00	230 00	198 00	1774 97	1 22	4 19
1924	44	140	83 8	100 29	48 22	4 08	13 00	285 00	272 00	2308 46	90	3 90
26	42	134	81 7	97 21	50 20	4 34	15 00	330 00	315 00	2501 28	1 82	7 71
28	40	135	84 4	103 00	54 36	4 68	30 00	360 00	330 00	2933 27	2 44	11 16
1931	37	121	81 2	97 73	50 72	4 61	25 00	310 00	285 00	2550 86	1 70	7 42
1934	34	118	83 7	82 11	42 11	3 88	15 00	320 00	305 00	1757 88	2 03	10 54
Total		1787	81 1	96 37	50 47	1 19	10 00	510 00	500 00	2546 04	2 01	10 03

1/ % investigated (examined) 2/ m_2 (1 1/N)s^2; b_1 $m_3/m_2^{3/2}$; b_2 m_4/m_2^2

Table A III 50

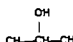
Health survey in the Reykjavik area Stage I 1967 - 68 - Men
Values (x_i) of total cholesterol in pooled serum

Date of extraction	Batch I			
	x_i	$x_{i+1}-x_i$		
1967 8 Dec	254 mg%		Number n	14
12	242	- 12	Mean $\bar{x}$	249 4 mg%
19	241	- 1	Variance s^2	61 96
21	250	+ 9	s d s	7 87
22	250	0	Min	238
28	238		Max	266
1968 4 Jan	266	+ 28	Range	28
5	248	- 18		
10	248	0		
11	258	+ 10		
16	255	- 3		
17	256	+ 1		
18	246	- 10		
19	240 241 1/	- 6		

1/ This value is not included in the statistical characteristics

ACCOMPANYING DOCUMENTS

Isopropyl Alcohol



propanol-2, Isopropanol, IPA IPS.1

Property	Test method	Specified limit
Purity % wt	By difference	99.7 min
Colour (Hazen units)	ASTM D1209	5 max
Relative density 20/20°C	SMS 1347†	0.786–0.787
Water % wt	ASTM D1364	0.15 max
Water miscibility	ASTM D1722	Completely miscible
Distillation range at 760 mm Hg	ASTM D1078	
IBP °C		82.0 min
DP °C		83.0 max
Acidity (other than carbon dioxide) as acetic acid % wt	SMS 277	0.002 max
Non-volatile matter g/100 ml	ASTM D1353‡	0.002 max

[illegible] Ketone (as MEK) determined by SMS [illegible]
†Shell test method
‡300 ml test sample
This product meets the requirements of BS 1595, ASTM D770, DIN [illegible], BP and USP

GENERAL INFORMATION

A. Hazard

Highly inflammable. The toxicity is low but continuous inhalation of vapour should be avoided. As with other organic solvents, prolonged exposure may cause irritation to the eyes, mucous membranes and throat.

B. Flash Point

50°F 10°C (IP 170 – Abel)

(continued overleaf)

Interpretation

About two thirds of apparently healthy normal adults show IMMUNOCRIT values from 1.5 mm to 2.7 mm. Those under 20 usually show values near the low end of this range, while those from the 50 and older age groups tend to be near the top of the range. In general, males show somewhat higher mean values than do females [illegible] the same age group. Details of studies of normal and pathological serum samples are available from Hyland Laboratories.

In spite of individual variations within the various age and sex groups, the IMMUNOCRIT value is remarkably constant for [illegible] given individual, untreated, [illegible] constant state of health. Once [illegible] have been established for an individual, changes due to progress of disease or therapy can be reliably followed.

Comments

1. It [illegible] not necessary to use [illegible] fasting specimen for BETA L TEST. For best results, the test should be performed on serum rather than plasma. The serum may be frozen, refrigerated, fresh, or [illegible].
2. Use the correct pipet or dropper for each purpose. Hold each vertically when delivering drops from it. Drop sizes are critical. Rubber bulbs are provided to facilitate control of drops from capillary tubes.
3. Use of the paper slides furnished [illegible] recommended as the surface of [illegible] plain slides does not always seem suitable for use in this test.
4. After mixing antiserum and patient [illegible] serum on the slide, [illegible] portant to fill the IMMUNOCRIT tube as quickly as possible so that the mixture of precipitate and liquid [illegible] the tube [illegible] representative of that on the slide.
5. When flame sealing [illegible] important to hold tube horizontally to keep contents from moving toward flame. Scorched or heat [illegible] [illegible] give inaccurate results.
6. Centrifuges providing [illegible] lower relative centrifugal force than those mentioned [illegible] Step 6 do not produce uniform packing of the precipitate even with prolonged centrifugation.

   Discard tubes showing evidence of leakage after centrifugation (appreciably shorter liquid column) and repeat test.
8. Occasionally precipitate may pack at top of column when centrifuged or may show outer [illegible] such precipitates are read and interpreted [illegible] the usual manner.
9. [illegible] important to be consistent [illegible] technic of performing the test (quality of flame sealing or use of plastic seal, position of capillary [illegible], etc.)
10. Rubber bulbs for capillary pipets are packed inside cap of container. To remove bulbs, take off cap, then squeeze top of cap between thumb and forefinger.

Other Uses — Other Methods

BETA [illegible] TEST antiserum may be used to obtain values for beta lipoprotein cholesterol by precipitating beta lipoprotein [illegible] test tube using larger amounts [illegible] antiserum and patient [illegible] serum, then proceeding with conventional cholesterol analysis of the precipitate.

The amounts and [illegible] distribution of cholesterol [illegible] the alpha and beta lipoprotein fractions have been obtained by performing micro cholesterol assays on the supernatant of the mixture of BETA L TEST antiserum and patient's serum and the patient's serum alone. The difference, after correction for cholesterol [illegible] the BETA L TEST antiserum, is the beta lipoprotein cholesterol.

The antiserum may be used for determining beta lipoprotein [illegible] fetal cord blood, urine, spinal fluid, etc., or in any procedure where immunologically specific precipitation of serum beta lipoprotein [illegible] desired.

Use of Drummond Microhematocrit Centrifuge

The Drummond Microhematocrit centrifuge uses capillary tubes 33 mm long, while the IMMUNOCRIT tubes supplied with the BETA L TEST are 75 mm in length and are filled to [illegible] total column height of 60 mm. However, the Drummond centrifuge may be used with the 33 mm capillaries instead of the longer IMMUNOCRIT tubes, by substituting the following after Step 3.

1. Partially (about two thirds) fill [illegible] Drummond capillary with the mixture of test serum and BETA L TEST antiserum, flame seal without scorching, and centrifuge for 5 minutes.
2. Measure, in mm, the height of the column of precipitate and the height of the total column.
3. Calculate the equivalent mm of IMMUNOCRIT precipitate using the following formula:

$$\frac{\text{height of precipitate column}}{\text{height of total column}} \times 60 = \text{equivalent mm of IMMUNOCRIT precipitate}$$

The results obtained with [illegible] Drummond centrifuge, when calculated as shown, are directly comparable with those obtained with the International and the Adams instruments, except that results obtained with the Drummond instrument may be slightly less precise because of the inherent [illegible] difficulty [illegible] measuring [illegible] shorter column of precipitate with the same degree of precision as [illegible] longer one.

References

1. [illegible] C. L., Fish, R. T., Fleishman, W. [illegible] Tuchs, A., Goodman, J. R., and Carpenter, C. [illegible] A simple method for quantitation of serum beta lipoproteins by means of the IMMUNOCRIT. Amer. J. Clin. Path. 35:222, 1961.
2. Bergquist, L. M., Carroll, [illegible] P., Jr., and Searcy, R. L.: Evaluation of [illegible] specific antiserum for serum beta lipoprotein estimation. Lancet 1:537 (March 11) 1961.
3. Searcy, R. [illegible] Carroll, V. P., Jr., and Bergquist, L. M.: Serum lipoprotein levels [illegible] Niemann-Pick disease. Lancet [illegible] (March 25) 1961.
4. Cheney, [illegible] L., Fish, R. T., Lee, K., and Carlson, Bert, Jr.: An immunochemical approach to beta lipoprotein analyses. Clin. Research 9:93, 1961.
5. Searcy, R. L., and Bergquist, L. M.: Biochemistry of serum lipoproteins [illegible] health and disease. Charles C Thomas, Springfield. To be published.

How Supplied

Hyland BETA L [illegible] TEST reagent list number 038 030
Patent No. [illegible]



HYLAND

BETA-L TEST®

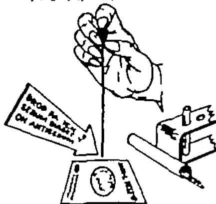
Hyland Antihuman Beta Lipoprotein Precipitin Serum is produced in animals by hyperimmunization with human serum beta lipoprotein isolated by ultracentrifugation. This antiserum has been processed to react specifically with beta lipoprotein and to produce rapid and complete precipitation of the low density lipoprotein (density less than 1.063 gm/ml).

Hyland Antihuman Beta Lipoprotein Precipitin Serum is recommended for use in rapid screening test for elevated serum beta lipoprotein levels by the DENTUROCRIT® method.[1,2,3]

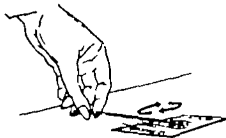
The antiserum contains sodium azide 0.1% as preservative, but care must be taken to avoid contamination. The antiserum should be stored between 2° and 8°C (35° to 46°F) when not in use.

Step 1. Using dropper in bottle, place two drops of Antihuman Beta-Lipoprotein Precipitin Serum on one of the paper BETA L TEST® slides provided.

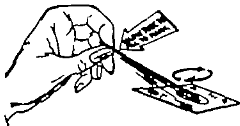
Step 2. Add one drop of patient's serum, using larger (unmarked) capillary tube with bulb attached. Hold capillary tube vertically to get proper drop size.



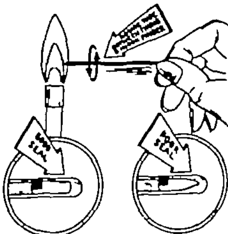
Step 3. Immediately thoroughly mix antiserum and patient's serum with toothpick or applicator held almost horizontally; use 10 to 12 circular strokes, spreading mixture over the indicated area on the BETA L TEST® slide.



Step 4. Holding marked end of DENTUROCRIT tube, quickly fill to bottom of mark. Important—move capillary tube through mixture while allowing tube to fill in order to obtain representative sample. Circular movement is again recommended for consistent results.

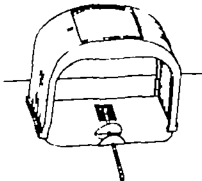


Step 5. Flame-seal empty end of tube (end near mark). Use same technique as when sealing hematocrit tube. Hold tube horizontally with tip at edge of lower portion of a hot flame to obtain flat glass seal bonds. As an alternative to flame sealing, various plastic seals may be used, provided no leakage occurs.



Step 6. Place sealed end of capillary tube toward outside rim of centrifuge and spin for 5 minutes. Use Adams Micro hematocrit, International Micro Capillary Centrifuge or other types with similar speeds and head sizes.

Step 7. Read length of column, estimating nearest 0.1 mm. For accurate consistent readings use viewer, tube holder and millimeter scale provided.



(3) Never use the high pump peed with two-speed pump

(4) During course of run keep reagent ealed ith parafilm to minimiz moisture pickup from the atmosphere

Operating Sequence:

(1) Pump water through manif ld for five inutes prior to operation During this time check for leaks pressure build-up pinched tubing poor connections etc

(2) Following w ter rinse lift ll reagent lines out of water llowing ir to fl sh through ystem for three minutes This prev nts bsequent mixing of acid with w ter hich would dev lop exces iv he t nd pressure

(3) Pl ce color reagent line in ts bottle and pump color reagent through ystem Sample line hould be purging ter from Sampler ll wash reservoir Isopropanol give lightly higher baseline than ter When reagent baseline is tabilized, set t 99% T th ter runn ng through sampl line Also heck 0% T and Recorder gain.

(4) F ll sample cups and place on covered tray to inh bit evaporation Alw ys place two cups of isopropanol before tandards t beginn ing f run

(5) At the end of the ru remov the gla aspirating line from the olor reagent by gentl pulling it through ad of pape towels Handle it caref ly it may pl tter id

(6) Allow r t flush through reagent and sample line for three minutes Then flush ter through ystem for t lea t seven nutes

A manif ld gee takes pumpi g holesterol color reagent ill discolor first becoming milky whit then dark brow Th is normal. If tub ng shows igns of naking tretch end blocks one notch Once endblocks have been tretched to the second and third notches do not return to the first notch

CHOLESTEROL REAGENTS

Cholesterol Color Reagent Anhydrous

Note All hemic l are J T Baker analytic l reagents xcept here other source is pecified

Chemical Composition:

1 Ferric Chloride Anhydrous R agent, powder s blimed (Matheson Coleman & Bell) 825 mg

2 Glacial Acetic A id conforming to Dichromate Test 2000 ml

3. Conc Sulfuric A id Reagent Grade 1000 ml

Preparation. In handli g and preparing holesterol color reagent minimize exposure f concentrated acids to tmospheric moisture Be ure to ear goggle and take necessary precautions in handling these conc ntrated acids

1 Place 1600 ml of glacial acetic acid in glas toppered 2 liter fl k. Add the ferric hloride quantitati ly W h powder ff neck of cylinder with 100 ml of glacial acetic acid. Stopper Place on thermomixer and tir ith gentle heating until powder dissolve

2. Allow solution to cool and bring to mark with additional glacial cid

3 Transfer sol tion carefully t 4 liter erlenmeyer flask. Add lfuric acid tw portions f 500 ml Mix by swirling after additions

4 Seal flask with luminum foil or para film Allow to cool

5. Transfer reagent to amber gla s bottle Reagent is stable for at lea t one month.

Isopropanol

Tech icon Formal AR-61-60 Reagent Grad Isopropanol

CHOLESTEROL STANDARDS

Stock Standard (5 mg cholesterol per ml)

Chemical Composition:

1 Cholesterol (E *tman Organic Chem icals catalog N 909)* 500 mg.

2 Isopropanol *(ACS reagent grade q.s)* 100 ml.

Preparation

1 Place 500 mg holesterol in 100 ml beaker Add pproximately 50 ml isopropanol

TECHNICON® AutoAnalyzer® METHODOLOGY



method file

N 24a

TOTAL CHOLESTEROL IN SERUM

GENERAL DESCRIPTION

This quantitative procedure for the determination of cholesterol is based on the reaction of concentrated sulfuric acid and ferric chloride in acetic acid with steroids having the 5-ene 3β-ol grouping

The automation of the col rimetric proce-*d re for cholesterol is described in an article* now in press by *Block Jarrett and Le ine* This new method logy is a modificatio of a previous procedure described by *J Levine and B Zak (Clin Chim Acta 10 1961 pp 381-84)*

A 1 in 20 extract of serum in isopropanol *is prepared An anhydrous color reagent con-*tai ing ferric chloride diss lved in a mixt re of acetic and sulfuric acids is used This re ge t is preheated to 95 C i a 40 foot gl ss coil After lea ing the heating bath the stream is *segmented with air and the serum e tra t in*troduced Th reaction takes place in vacuum j cketed mixi g c ils C lor is d vel ped nd read at 550 mμ in a 15 mm tubular flowcell The method is usable for cholesterol determin ation *ranging from 0 to 400 mg % the basis* of 1 in 20 stand rds

OPERATING PROCEDURE NOTES

Speed Samples are run at 40 per h ur Precision is slightly improved at 30 per hour

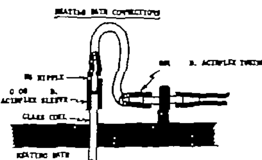
Manifold *(see flow diagram)*

(1) Standard pump tubes *are used for pump*ing reagent. A Solvaflex p mp tube is used for th ample line

(2) A 12 in length of 0 081 in I D Acidflex tubing is used to connect the be ting bath outlet to the H3 fitting This le gth hould not be xceeded *Change tubing when t shows* signs of swelling

(3) Supply distilled water to the Sampler II wash well Water gives a better wash between *samples than isopropanol*

Heating Bath Connections: Connect heating bath glass extensions as diagrammed below



*Flowcell M y be constructed of standard tub*ing

Preparatio of Extract: Add 9 5 ml of is propanol *(ACS reagent grad)* to a series of test *tube via an automatic burette Pipette 0 5 ml* of rum i to the isopropanol and cap the tube *Mix immediately to prod ce a finely di ided pre*cipitate Let tand f five minutes then filter or ce trifuge taking care n t to lose solvent by evaporation Th supernata t extract is then tored in stoppered tube until ready for use For analys s fill sample ps to the supporting l p otherwise i complete sample aspiration may result. Whe running a plate f s mples be sure to us the pl tic over pl te *to prevent* evaporation Sm ller q antities of erum may be used but be re to maintain the 1 in 20 *extract ratio*

Preca tions U e f highly concentrated acid olor reagent require several preca tions

(1) Wear glasses or *fety goggles*

(2) Be re to ha ufficie t flow of water flush g out the waste in drains

(3) Never use the high pump peed w th two-speed pump

(4) During course of run keep reagent sealed ith paraffin to minimiz moisture pickup from the atmosphere

Operating Sequence:

(1) Pump water through manifold for five minutes prior to operation During this time check for leaks pres ure bu ld-up pinched tubing poor connections etc

(2) F flowing water rinse 1 ft all reagent lines out of w ter allowing ir to flush through ystem for three minutes Th prevents bse quent mixing of acid with water which would develop exces ive heat nd pressure

(3) Place color reagent line in te bottle and pump color reagent through y tem Sam pl line hould be aspirating water from Sampler II ash reservoir Isopropanol gi es slightly higher baseline tha ater When reagent baseline is tabilized, set t 99" T th water running through sampl line Als heck 0" T and Recorder gai

(4) F ll sample cups nd place on covered tray to inhibit ev poration Alw ys place two cups of isopropanol before standards t beginning f run.

(5) At the end of the ru remov the gla aspirating l ne from the color re gent by gentl pull g it through wad of paper tow l Handle it caref ly it may platter acid

(6) Allow ir to flush through reagent and sampl l ne for three minutes Then fl h water through ystem for t lea t seven m nutes

A ma ifold gra tubes pumping holesterol olor reagent w ll d scolor first becoming milky white then dark brow Thi is normal. If tubing bows igns of making stretch endblocks one notch One endblocks have bee stretched to the second and third notches do not return to the first notch.

CHOLESTEROL REAGENTS

Cholesterol Color Reagent Anhydrous

Note All chemic l are J T Baker analytic l reagents except where other sourc is pecified

Chemic l Composition:

1 Ferric Chloride Anhydrous Reagent, powder blimed (Mathe on Col man & Bell) 825 mg

2. Glacial Acetic A id conforming to Dichromate Test 2000 ml

3. Conc Sulfuric A id Reagent Grade 1000 ml

Preparation In handling and preparing cholest rol color reagent, mi imize posure f concentrated acid to tmospheric moisture Be ure t wear goggles and take necessary precautions in handling these concentrated acid

1 Place 1500 ml of glacial acetic acid in glas toppered 2 liter flask. Add the ferric hloride quantitatively Wash powder ff neck of cylinde with 100 ml f glacial acetic acid. Stopper Place on thermomixer nd tir with gentle heati g until powde d ssol es

2 Allow solution to cool and bring to mark with additional glacial acid.

3. Transfer solution carefully to 4 liter erlenmeyer flask. Add ulfuric acid l tw por tions of 500 ml Mix by wirling after additions

4 Seal fl k ith lu num foil or parafilm Allow to cool

5 Transfer reagent to mber gl bottl Reagent is table for at lea t one month

Isopropanol

Technicon Formal AR-64-60 Reagent Grade Isopropanol

CHOLESTEROL STANDARDS

Stock Standard (5 mg chol sterol per ml)

Chemical Composition:

1 Cholesterol (*Eastman Organic Chem icals catalog N 909)* 500 mg

2. Isopropanol (*ACS reagent grade q.s.)* 100 ml.

Preparation

1 Place 500 mg holesterol i 100 ml beaker Add pproximately 50 ml isopropanol

Mix well and gently heat the isopropanol on a hot plate to dissolve the cholesterol

2 Cool and transfer the isopropanol-cholesterol solution to a 100 ml volumetric flask *Rinse the beaker with isopropanol transfer the* rinsings to the flask Dilute to mark with I o-propanol

3 Bottle in 4 oz amber glass bottle with plastic polyseal cap

Working Standards

1 Use volumetric glassware for prepara tion of the dilute standards

2 Use redistilled isopropanol for prepara tion of the dilutions

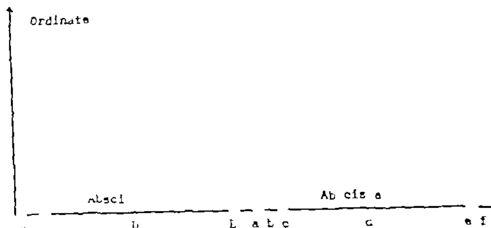
ml of Stock	Dilute to	mg Cholesterol per 100 ml
1	100 ml	5
2	100 ml	10
3	100 ml	15
4	100 ml	20

3 Bottle the dilute standards in 4 oz am ber glass bottles with plastic polyse l caps

Note The e standards are ba ed pon us ing a 1 in 0 isopropanol xtract in the ch les terol determination They corre pond to 100 200 300 400 mg cholesterol per 100 ml h n multipl ed by a dilution f ctor f 20

(flow diagram on ... fi

C m ts on th histogr m



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Ex The β-lipoprotein values in the interval

$$]0\ 9 + 0\ 3(k-1) \quad 0\ 9 + 0\ 3k]$$

are presented by the k-th column on the main part D k= 1 15 Values ≤ 0 9 make up the column supported by part B and results > 5 4 make up the column supported by F

Comments on the fractile-diagrams

Let G(x) denote the standardized cumulative normal distribution function

Ex 1 Let H(x) denote the (empirical) cumulative distribution function of the β-lipoprotein values

The computer plotted in a coordinate system points (×) with coordinates

$$(1\ 2 + 0\ 3k \quad 5 + G^{-1}\ H(1\ 2 + 0\ 3k))$$
$$k = 0 \qquad 14,$$

if H(1 2 + 0 3k) lay in the interval]0 005 o 995[
The values (1 2 + 0 3k) k= 0 14 are the right endpoints of the subintervals of part D (see Comments on the histograms)

Ex 2 Let I(x) denote the (empirical) cumulative distribution function of the logarithm of β-lipoprotein values

Ca 1/15 of the difference between the logarithms of the endpoints of part D corresponds to the interval size in Ex 1 In this case the width 0 05 was chosen and the points plotted were

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$$(0\ 00 + 0\ 05k\quad 5 + G^{-1}\ I(0\ 00 + 0\ 05k))$$
$$k = 0 \qquad 1$$

Acta Medica Scandinavica

Supplementum 617

Management of Hypertension

Clinical and hemodynamic studies with special reference to patients refractory to treatment

By Ove Andersson

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

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By

Ove Andersson



GÖTEBORG 1977

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INTRODUCTION

The prese t study is concerned with the management of hypertension A model for the management of large numbe of hype tensive patients is presented F r this purpose *description is given of the organi ation* nd function of experimental out patient hyperten ion cli ic Special i te st has been devoted to p oblems su h as the pos ibility of reducing blood pressure to an acceptable level i a majority of hypertensi e cases deri ed from sc eening of a t tal population sampl F rthermo e impor tant cli ical con iderations i the treatment of hypertension i sid ffects of the the py and pati nt dhe ence ha been studied

Anothe impo tant conside tion cove ed i the pr se t study i the pre a lence of second ry c able forms of hypertension i uns lected hyperten si patients as uch res lts should i fluence the routines for the diagnostic work-up

Ref act ry primary hype tension a condition e but difficult to ha dle and dangerou for the patients is one of the majo concern i this study Consequently hype tensi patients r fract ry to triple drug t eat ment ha e bee investigated by means of cent al and periphe al hemodynamics They ha lso been t at d i accordance with the findi gs of these inve tigations and the s lts a p ese ted

generally been 70 85 % Such st dies ha e shown that about half of the hypertensive population is unaware of their blood press re elevation and hence untreated Of the treated patients a majority has an inadequate blood pressure control A substa tial part has previously been on treat ment but has discontinued the medication Certain studies indicate a drop-out rate from antihypertensi e therapy of 50 % per year (7 84)

This is the background for the growing interest in procedures aimed at finding and treating all patients with the disease F rthermore a new esponsibility for the continuous follow-up of the patie ts is developing Fo this reason systems and o ga izations fo bette management of hyper tension i the community are tested at p esent (35 71)

Pr alence of second ry hype ten ion

A e iew of the lite atu on econdary forms of hype tension shows a p e alence of about 10 % in select d s ries (18 22 33) However the propor tion of the tot l hype tensive population with demonstrable ca es of hy pe t sion i not known It is concei able that v riation due to age sex and thnic and acial differenc s may exist It is important to establish the p evalence of secondary hype tension ince the diagnostic work-up should la gely be imed t detecting s rgically cu able forms of hyperten-sion Thus the design and scope of the i stigations re depending on the xpected number of c ses with secondary hype tension Repo ts from standa di d wo k up of unselected patient series homogeneous in age and sex not existing at p esent

Ref act ry hypert sion

The e is no lea defi ition of the term efractory hype te sion' The general meaning f the t rm howeve implies patients resistant to nti hype te sive the py

Poor blood p essu e esponse to single drug t eatment associated with so-dium etention and expanded extracell la fluid volume has previously been po ted (19 23) In these studies blood p e s e was well cont olled af t addition of di etics Combined therapy with two o mor drugs is also common and many author point out the adva tage of ffective blood pres

PREVIOUS STUDIES

General aspects on the benefit of antihypertensive treatment

Hypertension of primary or secondary origin has been shown to be an important factor in the development of cardiovascular diseases (45 46 77 87) Thus it was reasonable to assume that treatment of hypertension might eliminate or reduce morbidity in hypertensive cardiovascular diseases

The earliest proof of benefit from antihypertensive treatment was the demonstration of an improved prognosis with respect to survival rate in patients with malignant hypertension (57 63 66 69) Shortly thereafter communications from Smirk s group showed an improved prognosis for patients with congestive heart disease or grade II eye-ground changes among treated hypertensive patients (40 70) The prevention of cerebral vascular disease by hypotensive treatment was convincingly demonstrated in several studies (4 41 48) A well controlled study in a selected population of male hypertensives gave evidence of a decrease in the frequency of complications such as congestive heart failure cerebrovascular accidents and renovascular disease in the treated patients The patients had moderate to severe hypertension with a high frequency of organ damage at entry (79 80)

Further studies are needed to evaluate the benefit from treatment of hypertension in elderly in women and in mild hypertension without hypertensive organ involvement Furthermore no valid proof of primary prevention of myocardial infarction or sudden death by ant hypertensive treatment exists at present

A new attitude concerning management of hypertension

Epidemiological st dies have generally shown a prevalence of hypertension of 5 20 % (42 76) The participation rate in the screening examinations has

generally been 70 85 % Such studies have shown that about half of the hypertensi e population is unaware of their blood pressure elevation and hence untreated Of the treated patients a majority has an inadequate blood pressure control A substantial part has previously been on treat ment but has discontinued the medication Certain studies indicate a drop out rate from antihypertensi e therapy of 50 % per year (7 84)

This is the background fo the growing interest in procedures aimed at finding and t eating all patients with the disease Furthermore a new responsibility fo the continuous follow-up of the patients is developing F r this e son systems and organizations fo bett r management of hype tension I the community a e test d at present (35 71)

Pr lence of secondary hype te sion

A review of the lite at e on secondary forms of hype ten ion shows a pre alence of bout 10 % in selected se i s (18 22 33) Howeve the propo tion of the tot l hyperten ive population with demonstrable causes of hy-pertension is not known It is conceivable that ari tion due to ag sex and thni and racial diffe ences may exi t It i import nt to establish the p evalence of secondary hype tension ince the diagnosti work-up should l rgely be imed t detecting su gically curable forms of hype ten ion Thus the design and scope of the inv stigations a e depending on the xpect d numbe of ca e with secondary hypertension Reports from standa dized work up of unsele ted patient seri s homogeneous i age and sex r not isting at present

R f actory hypertension

The e i no cl a definition of the te m refractory hypertension The gene al meaning of the t m howeve impli s patients resistant to anti hype ten i e the py

Poo blood p ssu e esponse to single d ug treatment associated with so-dium etc tion and expanded ext acell l fluid volume has p eviously been epo ted (19 23) I these studies blood pressu e was well controlled af te addition of di tics Combined therapy with two or mo e drugs is also common a d many autho s poi t out the ad antage of effective blood pres

sure reduction (37 89) However also with combined therapy some patients respond inadequately Reports on the prevalence of this type of refractory hypertension from large treated populations are lacking

In a definition of refractory hypertension it would be logical to take in to account the blood pressure reduction the blood pressure level achieved and the amount of drugs used Consequently in the present study the term refractory has been used in patients on triple drug therapy in doses regarded as optimal in our clinic with blood pressures still above 200/110 mm Hg and a blood pressure reduction of less than 10 %

Vascular peripheral resistance in arterial hypertension

It is generally accepted that vascular resistance in patients with estab lished primary hypertension is increased while cardiac output is within normal range (27 28 51 64) In early stages i e border line or labile hypertension however cardiac output might be increased as the main hemo dynamic characteristic (43) The underlying mechanism by which vascular resistance is elevated is under discussion and several explanations have been proposed

The role of the sympathetic nervous system for the increased vascular peri pheral resistance is not yet quite clear (30) Normal increased and decreased activity of sympathetic origin by means of urinary or plasma cathecholamines has been shown (12) The sympathetic nerve activity has been shown to be increased (11 50) especially in early phases of hypertension (44) and decreased in later more severe hypertension (5 29) Therefore the contro versy is probably due to differently selected patient materials

Another factor of importance for vascular resistance is blood viscosity It has been reported that patients with primary hypertension have increa sed blood viscosity (75) Other investigators consider blood viscosity to be within normal limits in essential hype tension This might simply be a question about methods since in vitro measurements a e unreliable indica tors of in vivo viscosity (13)

A plausible explanation of the increased vascular resistance in hyperten sion is the concept of a morphologic change in the arteriolar wall Animal

studies from Folkow and his group hav demonstrated that vasculer flow re- si tance is inc eased in hype tensive rats even at ma imal flow asodila tation when compa ed to normotensive ats fact strongly suggesting re duced ascular lumina in these animals Furthermore for any gi en degree of smooth muscle sho tening the curve fo blood flow r sistance will be steeper in v ssels with an incr sed wall/lumen ratio s compared to nor mal vessels (25) These observations re also confirmed in man (26 67) This might be one o even the main explanation fo the inc eased 'vas cular reacti ity' to asoconst icto gents often found in hypertensi e patients (14 16 56) The normal threshold of flow esistanc increase on i fused vasocon trictor agents in hype tensi e patients (67) contradicts the theory of an increased 'vascular reacti ity' in the sense of increased arteriol smooth mu cle ensiti ity

V sodilating the apy in hype tension

Di etic drugs apparently reduce arterial pressu e by dec easing both tot l pe iphe l esistanc and e t acell la fl id and plasma volume (10 74 78) U f tunately thei hypotensi e action is athe weak and sufficient only i mild hypertension

Sympathoplegic d ug elax both esistance and capacit nce essels and can dep myoca dial funct on (65) Do e d pendent impairme t f sympa thetically med ated homeostatic ca diovascula efle es can caus o tho- static and ex ise hypotension and i terf ence by these drugs with othe ympathetic f nctions can also cause ga t oi testinal and sexual di t bances

Di ect asodilati g d ugs like hyd ala ine ha the ad antage of acting i blood el and almost exten i ely on a te ioles while venous capa c tanc i t ely unaffe ted (90) Howev if not sed i combina t on ith ad ene gic blocking d ugs hyd lazine must be considered i t vely neffe ti e the t atment of hype te sion Hyd lazine alone would nc te be ecepto efle acti ity esulting i inc eased sympa thet outflow inc ase ca diac output and thus limit blood p ssu e re duct on (26 90) On the othe hand in combination the py with β eceptor blocke hyd lazine has p oved to give effecti blood p ess re reduc tion (37 89) Hyd alazine is gener lly well tol ated i doses of 150 200

mg per day This dose should however rarely be exceeded because of an increased risk of developing a lupus erythematosus resembling syndrome in patients with low metabolisation rate of the drug (58)

Minoxidil a piperidino pyrimidine derivative is still under clinical investigation Like hydralazine this drug acts by direct relaxation of arteriolar smooth muscle (15 61) and is probably superior to hydralazine in this respect (36) It has sodium retaining properties and should there fore be administered together with diuretic drugs (34 36) β adrenergic blockers must also be given for the same reason as with hydralazine Right atrium cardiotoxic lesions in dogs are described and some patients develop different degrees of hypertrichosis (15 36) In spite of a minor risk of cardiac lesions never reported in man minoxidil has gained interest be cause of potent vasodilating properties necessary especially in severe hy pertension

AIM OF THE PRESENT STUDY

The aim of the p sent st dy wa to

describe the o ganization of an out patient hypertension clinic and to p esent long term ults of blood press e reduction frequency of side-effect and patient adherence in a random popul tion sample of hype te sive middle aged men

est blish the prev lence of secondary hype te sion in a andom sample of middle- ged me in o de to get background data for de t rmination of the scope of diagno tic i vestigations needed in such hype tensi e populations

i vest gate the cent l and pe ipheral hemodynamic characteristics of patients with efractory hype tension i ord r to find a reason f the poo spons to the apy

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PATIENTS

A multifactor primary prevention trial was started in Göteborg in 1970 (85) The intervention group consisted of a randomly selected third of all men aged 47 54 years at entry (born in 1915 1922 or 1924 1925) and living in Göteborg (n=9996) Of the 9996 subjects invited 7455 (75 %) attended the screening examination which included determination of blood pressure smo king habits and cholesterol Cut off points for hypertension was systolic blood pressure above 175 mm Hg or diastolic blood pressure above 115 mm Hg at the screening examination and at a re examination after 1 2 weeks Pa tients with current antihypertensive therapy were also invited to follow-up

Out of 7455 subjects examined 1159 (16 %) had either antihypertensive the rapy (n= 361) or a blood pressure at the first visit exceeding one or both of the cut off points (n=798) The latter group was invited for a re examina tion and 324 (41 %) of them had blood pressures below the limits on this occasion (Table I) Fifty eight patients did not attend the re examination for various reasons Out of 361 patients who were already receiving anti hypertensive treatment 39 had already appointments for follow-up with their physicians Fifty two patients either declined further treatment or did not show up for follow-up Consequently out of 835 patients considered hyper tensive 686 (82 %) accepted the invitation and attended the hypertension clinic Results from these patients are presented in papers I II

After three years treatment 20 patients had blood pressure above 200 mm Hg systolic and 110 mm Hg diastolic on triple drug regimen and were regarded having refractory hypertension Five of these did not consent to the hemody namic study planned Two patients were found to take the drugs irregularly as shown by negative tests for fluorescein in the urine Two patients had secondary hypertension The remaining eleven patients were examined with central and peripheral hemodynamics One examination failed for technical reasons Results from the remaining 10 patients are presented in papers III IV

Table I The f te of s bjects with blood p ess re above 175 and/or 115 mm Hg or current antihype te sive tr atment at screening (n 1159)

Untre ted (n=798)	
SBP 175 and DBP 115 at e-examination	324
Ref s d to participat	21
Dead or mo ed	7
Othe cau es (mi sed f il r to comply tc)	30
Refer ed to the hype tension cli i	416
Treated (n=361)	
F ef ed own physician	39
Refu ed to particip at	24
Dead o moved	9
Othe ca ses (missed fail re to comply etc)	19
Refe ed to the hype tension li ic	270

METHODS

THE SCREENING EXAMINATION

The screening examination in the primary prevention trial was performed in the afternoon between 4 30 and 7 00 p m The blood pressure measurement was done by physicians It was measured after a 4 5 minutes long interview concerning the subjects physical health and with the subjects sitting The blood pressure was measured in the right arm A cuff containing a rubber balloon 12 cm wide and 26 cm long connected to a mercury manometer was used Diastolic blood pressure was recorded as phase 5 (disappearance of sounds) The measurements were recorded to the nearest 2 mm Hg

Cut off points for hypertension was blood pressure above 175 (SBP) or 115 (DBP) on two separate occasions within two weeks These patients but also those already on antihypertensive treatment were referred to the hypertension clinic Subjects with blood pressure 160 174 (SBP) or 95 114 (DBP) at the first or second examination were invited to annual re examinations and were subsequently referred to the hypertension clinic if they fulfilled the criteria mentioned

THE HYPERTENSION CLINIC

Organization

An out patient clinic for hypertensive patients was started at Sahlgrenska Hospital in 1970 The main objectives were

To treat and follow the hypertensive patients in the primary preventive trial

To be a referral center for patients with hypertension responding inadequately to therapy or having serious side effects during antihypertensive treatment

To constitute a research unit for epidemiological clinical and experi mental studies on arterial hypertensive disease

The hypertension clinic is located in the out-patient premises of the Department of Medicine I The f ll time personnel consisted of three spe cially trained nurses and one secretary All blood press re mea urements coll cting of blood samples as well a pa t of the history taking were done by the nurses The sec eta y had a key role i administrating the follow-up She also contacted patients who had failed to attend follow-up f ord t arrange new appointments Nine doctors with a pecial interest i arterial hyperte si disease one weekly half-day clinic each The patients generally saw the same doctor o nurse on each visit The clinic wo ked almost excl sively on an out patient basi

Blood p e su es

Routine blood press s t the hype tension cli ic were measured by nurses The blood p essure was egi tered i the supine position afte 5 minutes est and afte one minute i the standing position It was meas red in the right arm (at the fi st examination in both arms and the right leg) and eco ded to the nearest 2 mm Hg The diastolic blood p essure was e- co ded as pha e 5 i e when the sounds disappea ed A c ff (12 x 26 cm) connected to a mercu y manometer was sed The heart rate was measured immediately befo e the blood p e s e measurements in supine position

Diagno tic examination and follow-up

All pati t went th ough the same examination The e aminations were do ne tepwise and ta ted with two isits to the nu ses fo measu ement of blood p es and hea t ate sually with fo tnight between the ea d ng Du ing this time chest X rays and lect oc diog ams were done and sample fo blood nd ine tests we e taken The blood tests were hemoglob n sedimentation to S-electrolytes S creatinine S bilirubin S lkal ne phosphatases S ASAT (GOT) and S ALAT (GPT) S-urat S-choles t l and S t iglyce ides The rine tests we : protein glucose sedi ment and smolality afte 13 hou s thirst If abnormal osmolality was found a asop essin tannate test was done Isotope enography was car ied out i all men born 1915 1916 1920 and 1921 (n=287) u ing the standard

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THE SCREENING EXAMINATION

The screening examination in the primary prevention trial was performed in the afternoon between 4 30 and 7 00 p m The blood pressure measure ment was done by physicians It was measured after a 4 5 minutes long in terview concerning the subjects physical health and with the subjects sitting The blood pressure was measured in the right arm A cuff contai ning a rubber balloon 12 cm wide and 26 cm long connected to a mercury manometer was used Diastolic blood pressure was recorded as phase 5 (dis appearance of sounds) The measurements were recorded to the nearest 2 mm Hg

Cut off points for hypertension was blood pressure above 175 (SBP) or 115 (DBP) on two separate occasions within two weeks These patients but also those already on antihypertensive treatment were referred to the hyper tension clinic Subjects with blood pressure 160 174 (SBP) or 95 114 (DBP) at the first or second examination were invited to annual re examinations and were subsequently referred to the hypertension clinic if they fulfilled the criteria mentioned

THE HYPERTENSION CLINIC

Organization

An out patient clinic for hypertensive patients was started at Sahl grenska Hospital in 1970 The main objectives were

To treat and follow the hypertensive patients in the primary preven tive trial

- To be a referral center for patients with hypertension responding in adequately to therapy or having serious side effects during antihyper tensive treatment

To constit te a esearch unit for epidemiological clinical and experi mental studies on a te ial hypertensive disease

The hypertension clinic is located in the out-patient premises of the Department of Medicine I The f ll time personnel consisted of three spe cially trained nurses nd one secr tary All blood pressure measurements collecting of blood samples as well as part of the history taking were done by the nurses The sec etary had a key role in adai ist ating the follow-up She also contacted patients who had failed to attend follow-up in order to ar ang new appointments Nine doctors with a special interest in arte ial hypertensive disease ran one weekly half day clinic ea h The patients generally saw the same doctor or nurse on each isit The clinic worked almost excl si ely on a out patient ba is

Blood pressu es

Routine blood p ess res t the hypo tension clinic we e measured by nurses The blood p essure was egistered in the supine position afte 5 minutes est and afte one minut i the standing position It was meas red in the ight arm (at the fi t examination i both arms and the ight leg) and eco ded to the nea est 2 mm Hg The diast lic blood pressure was re co ded as phase 5 i e when the sounds disappeared A c ff (12 26 cm) connected to me c y manomete was used The hea t ate was measured immed at ly befo the blood pre sure measu ements in supine position

Diagno tic examination and follow-up

All patient we t th ough the same examination The examinations we e do ne t pwi and st ted with two isits to the nu ses fo measurement of blood p and hea t te sually with a f tnight between the rea ding Du ing thi time chest X ays and electroca diograms were done and sampl fo blood and ine te ts we taken The blood te ts were hemoglobi sedimentation te S-elect olyte S-c eatinine S bilirubin S lkal ne phosphatase S ASAT (GOT) nd S ALAT (GPT) S-u ate S-choles terol and S t iglyce ides The urine tests we e protein gl cose sedi ment and osmolality afte 13 hou s thirst If abnormal osmolality was found a asop e si tannate test was done Isotope enography was ca ried out i all men bo n 1915 1916 19 0 nd 1921 (n=287) using the standard

method and apparatus (Nucab Sweden) Intravenous pyelography In most cases rapid sequence pyelography was performed when the history blood or urine samples or the isotope renogram indicated a suspicion about se condary hypertension Thus intravenous pyelography was performed in 52 cases during the initial work up Renal arteriograms to confirm renal vascular disease was performed in 12 case Urinary catecholamine excre tion rate was determined in all 58 men born in 1921 using a method descri bed by von Euler and Floding (20)

In all 20 patients considered refractory to treatment during the third year of follow-up additional diagnostic examinations were carried out in order to identify patients with secondary hypertension Thus renal arte riograms were performed in 15 patients and isotope renograms or rapid e quence pyelograms were done in the remaining 5 patients

At the third visit to the clinic the patients were also examined by a physician who decided whether further diagnostic examinations were needed Drugs were prescribed and plans were outlined for further management Data from this third visit were used for comparison with follow-up data

After the initial phase patients with uncomplicated and adequately con trolled hypertension saw the physician once or twice a year Blood pres sure controls were done by the nurses at 3 6 monthly intervals For pa tients with problems of any kind the intervals between controls were adap ted individually If needed the patients could get in touch w th their physicians via the secretary at the clinic

Data were recorded in a standardized manner for scientific purposes Special data record forms were used for direct coding and compute ization

Indications for antihypertensive therapy

Antihypertensive treatment was introduced in

1 Patients between 40 and 60 years with repeated blood press res above 170/105 at rest Under the age of 40 and above the age of 60 the cor responding blood pressure levels have been 160/95 and 180/110 espec tively The same blood pressure limits were used for men and women

2 Patients with blood pressures below the above mentioned limits if heredity factors hypertensive organ manifestations or other risk factors for cardiovascular disease implied an inc eased risk These decisions have been made at the discretion of the physician

The aim of the antihypertensive therapy was to reduce the blood press re to what has been conside ed normal for the patient I under the age of 40 a blood p essure below 150/90 mm Hg between 40 and 60 years of age below 160/95 and above 60 yea s below 170/105 mm Hg

Choi e of antihype tensive drugs

The first d ug of choice has bee a β adrenoreceptor blocking agent in do es co esponding to propranolol 80-640 mg/day Thiazide di etics and chlo thalidone have also been common p eferably used in older patients with se ere hype tension where cardiac decompensation was found or anti cipated Diuretics have been sed in doses corresponding to 25 75 mg of hydrochlorothiazide per day A combination of drugs has gener lly been prefe ed athe than an excessive inc ea e i the dosage of one ingle d ug If ac eptable blood pressu e levels were not achieved with the ini tially gi en β adrene gic blocke and/o a di retic hydralazine (75 200 mg/day) ha been added If the combination of these drugs did not esult i adequat blood p essure eduction pironolactone bethanidine o occa ion lly high dose f rosemide o minoxidil has been added

Aft two yea follow-up t the cli ic 589/624 (94 4 %) patients were on antihype te si d ug the apy 32 % of the patients received single d ug and 68 % combined d ug the apy Thus 18 % of the patients had diu- t cs and 14 % of the patients had β ad enorec ptor blocking drugs The comb nation of di tic and β ad energic blocke s was given i 26 % and ad ene gi blocke and hyd lazine i 24 % of the patients 14 % had t iple d g combination consisting of di etics β adrenergic block and hyd alazine while 4 % had other drugs or d ug combinations

Regi t ation of ad se drug ffect

Withd awals f d ug caused by supposed side-effects were registered at the end of year one and yea two A ret ospective analysis of a possible causal lationship betwe drugs and adve se effects was made by the kin

the case records The judgement of causality was based on laboratory tests, subjective symptoms or signs related in time to the institution of treatment and recovering after withdrawal Provocation tests were not used The analysis was done by the author

INVESTIGATIONS IN REFRACTORY HYPERTENSION

Study plan

Ten of the patients (Group A) refractory to the triple drug treatment with thiazides (hydrochlorothiazide 50 mg daily or bendroflumethiazide 5 mg daily) propranolol 360 480 mg daily and hydralazine 150 225 mg daily were selected and checked for drug defaulting They were examined in accordance with our routines but renal arteriograms determination of glomerular filtration rate (6) and urine examination of VMA were also performed None of the refractory patients had a mean arterial pressure reduction of 10 % or more nor were their blood pressures at the clinic below 200/110 mm Hg

Another ten patients (Group B) had triple drug therapy and doses as the refractory patients but responded satisfactorily i e they showed mean arterial pressure reductions of 20 % or more and blood pressures at the clinic below 180/100 mm Hg They were examined according to the same routines and had the same additional diagnostic work-up as the refractory patients Each patient responding to therapy was selected to match a non respondor for sex age weight and renal function as well as untreated blood pressure during their first or second visit to the clinic

All patients in both groups had primary hypertension and they had eye ground changes corresponding to Grade II of the Keith Wagener and Barker classification Further patient data are presented in Table II

The patients in both groups were checked for drug defaulting and had isoproterenol infusions to estimate the degree of β adrenergic blockade Their acetylation phenotype was determined Subsequently plasma volume determinations and hemodynamic studies were performed

t bl ll Age height weight glomer la filt ation at (GFR) p etr tment auscultatory mean t ri l blood p ssu e (MAP_A) heart ate (HR) and heart siz (X ay) i refractory patie ts (G oup A) and pati t sponding to triple drug the apy (Group B)

Patient		Age (ye s)		Height/weight cm/kg		GFR (ml/mi m^2)		Pret atment MAP_A (mm Hg)		Pr treatment HR (beats/min)		Heart size (ml m^2)	
A	B	A	B	A	B	A	B	A	B	A	B	A	B
KR	AN	54	50	173/105	179/102	89	79	153	156	74	72	610	480
KEW	SG	52	53	174/90	175/92	74	84	156	155	80	70	500	435
KES	SM	59	55	172/100	179/99	89	75	153	153	90	92	440	490
LW	TB	52	54	179/90	171/91	8	86	162	160	76	102	590	470
EL	HA	60	59	176/79	175/76	74	72	153	141	97	76	600	520
EE	OR	57	59	174/95	175/94	72	72	160	159	84	86	470	480
BN	BGN	57	55	178/83	184/86	80	78	145	147	76	94	470	460
OK	DE	58	55	179/92	169/88	82	76	147	145	56	79	410	470
EA	SW	57	55	177/88	177/86	86	88	155	155	68	72	460	470
RS	EG	50	52	174/98	175/97	79	81	143	145	84	84	600	510
Mean		55 6	54 7	176/92	176/91	81	79	153	152	79	83	515	479
SD		3 37	2 79	2 5/7 8	4 2/7 6	6 1	5 6	6 2	6 6	11 5	10 8	76 8	24 3
Sig ifica ce		ns		ns		ns		ns		ns		ns	

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INVESTIGATIONS IN REFRACTORY HYPERTENSION

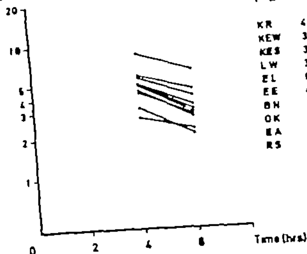
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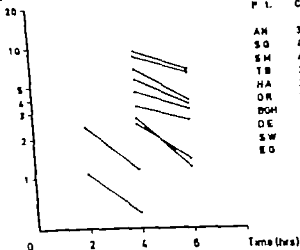


Fig 1 The esult of the Isoniazid acetylation phenotyping i ten patients ef actory to triple drug tr atment (upper part) d to patients sponding to triple drug tr atment (lower pa t) P tient I iti ls and Isoniazid plasma concentration half ti a e tabelled to the right Note thet fi e patients pondi g to tr tne t we e co side ably fast r acetyl tors tha any of the patient i the ref actory group

Detection of drug defaulting

All patients defined as refractory to triple drug treatment and occasionally other patients responding inadequately to treatment were given additional placebo treatment with riboflavin (riboflavin 15 mg Beviplex forte® Ferrosan) A qualitative assessment of riboflavin in fresh urine irradiated with ultra violet light by visual observation of a yellow fluorescence was then possible (79)

Determination of acetylation phenotype

The acetylation phenotype in the twenty patients investigated hemodynamically was determined isoniazid (1-isonicotinyl hydrazine Tibinide® Ferrosan) being metabolized in the same manner as hydralazine (21) was used The patients fasting ingested isoniazid 10 mg/kg body weight in the morning Venous samples were drawn after 2 4 and 6 hours The plasma was immediately separated and stored at 20° C until the analysis was performed The analysis was based on measurements of optical density in a spectrophotometer (53) Plasma concentration half time of isoniazid was based on the concentrations after 4 and 6 hours in all cases but two where low concentrations allowed only values after 2 and 4 hours

The results are illustrated in Fig 1 All patients refractory to treatment were shown to be slow acetylators according to plasma half time In the patients responding to treatment five patients were fast acetylators In two patients (DE SW) however the concentration of isoniazid after 2 hours was low and resorbtion failure or inappropriate dose ingested must be questioned

Isoproterenol infusion test

In order to estimate the degree of β adrenergic blockade isoproterenol in saline solution was infused intravenously (38) in the twenty patients who underwent central and peripheral hemodynamic investigations With the patients resting comfortably in the supine position and during continuous monitoring of the heart rate with ECG the infusion was started Initially an isoproterenol infusion rate of 1 µg/min was used After 3 minutes the infusion rate was increased to 3 µg/min and after another

electrocardiog am from which the heart rate was calculated were recorded on a Mingograph 81 (Siemens Elema) Intra arterial mean pressure (MAP) was obtained from electrically damped curves and measured immediat ly befo e each cardiac output determination Simultaneous direct and indirect bra chial artery pressures were determined initially Auscultatory pressure was recorded in the right arm and diastolic pressure was d termined as phase 5 Mean auscultatory arteri l pressure (MAP_A) was calculated as the diastolic blood press re 1/3 of the pulse pressure

Cardiac output was dete mined by the indicator dilution techniq e using a Cardiognost® (Atlas) and Indocyanine Green (Ca dio-Gre n®) The blood was reinf sed afte each determination and the mean from five se pa ate determinations was s d Stroke volume (SV) was calculated by divi ding cardiac output (CD) by hea t rate (HR) Total peripheral resistance (TPR) was obtained by di idi g mea intra a terial blood pre sure in the b achi l artery (MAP) by cardiac output It was expressed i arbitrary units (U) CO TPR and SV were corrected fo body surface area (BSA) and the following indicies CI TPRI and SVI we e deri ed

Regi nal scul r e istance

Hand blood flow determinations were sta ted two hou s fte the end of the ce tral hemodynamic i stigation One hou befo e flow d terminations and du ing the whole expe iment the patients were indirectly he ted until i te se pe spi ation i o der to abolish the sympathetic vasoco st iction acti ity t the k sels (60 b 62) Hand blood flow ('sympathoplegic flow') wa the det rmi d by enous occl sion plethysmog phy and blood p ssu eco ded i t a art rially i the cont alate l brachial tery The wate tempe at e in the plethysmograph was initially kept at 33° C and fl e eco ding of blood flow with simultaneous readings of blood p su we e done The flow sistance du ing these circumstanc s was d ignated ympathopleg sistance' (R_{symp}) The pl thysmog aph tempe- t r wa then inc ased to 43° C After about 3-4 minutes of arterial oc l on d ing which the patients exercised their hand muscles until ischem pai anothe 5 flow reco dings were done F om the highest flow alue and the cor esponding me n arte ial blood pressure i t nc t ma imal dil t tion 'mi inal esistanc (R_{mi}) was calculated and the mean of th ee separate det rminations of this flow and r sistance

3 minutes to 6 µg/min The heart rate after 3 minutes of the infusion rate at 6 µg/min was compared to the initial unstimulated heart rate

A minor but significant increase of the mean heart rate in the twenty patients was noted 2 1 beats/min ($p < 0\ 001$) The heart rate increase in refractory patients (Group A) was 2 5 beats/min and 1 9 beats/min in patients responding to treatment (Group B) the difference not being significant No patient had a heart rate increase exceeding 4 beats/min

Plasma volume determination

Plasma volume was determined in the refractory patients and their matched responding controls In the ten patients refractory to triple drug treatment plasma volume was also determined after blood pressure reduction on minoxidil treatment

Plasma volume was determined in the morning after 30 minutes rest in the supine position The patients had a light breakfast but were not allowed to smoke before the experiments They had taken their antihypertensive medication immediately prior to the resting period Evans Blue was injected and blood samples were drawn 5 10 15 and 20 minutes after the injection On the first determination the blood samples were drawn from a central venous catheter but on the re examination during minoxidil treatment from a peripheral antecubital vein Plasma concentration of the dye at zero time was estimated from a plot log concentration against time From that concentration and the originally injected amount of dye plasma volume was calculated (47)

Central hemodynamic studies

The hemodynamic studies were performed in the morni g and the patients had taken their antihypertensive medication about one hour earlier

Polyethylene catheters were inserted percutaneously into the left brachial artery and into a cubital vein The venous catheter was advanced to the right atrium or centrally in the superior caval vein and the position was checked with X ray The intra arterial blood pressure was recorded with a pressure transducer (Emt 34 Siemens Elema) This pressure and the

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Regional scula resistanc

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acceptable blood pressure (below 170/105 mm Hg) was achieved

During the first two months the patients were examined every week concerning blood pressure heart rate weight and side-effects Later these examinations followed every month S-electrolytes and S creatinine were followed every month

Plasma volume determinations and peripheral blood flow xaminations of the calf were done when the patients had achieved acceptable blood pressure control The results were compared with those achi ed on the pre ious therapy

STATISTICAL METHODS

Standa d methods we e used for calculati n of the mean (x) the standard deviation (SD) the linear correlation coefficient ( ) and the ariation coefficient The hypothesis of no difference in means was te ted with t test for pai ed obser ations In the comparisons between patients efractory to t eatment and thei matched controls t t st for independent data was used The hypothesi of no difference i proportions betwe n two groups was t t d with the χ squared te t O ly two tailed tests we e sed and diffe ences we e con de ed significant for p-values of 0 05 or less

was used The ratio between blood flow resistance at rest and that during maximal vasodilatation will be referred to as sympathoplegic tone as it is regarded to reflect the extent of smooth muscle contraction of the resistance vessels in the hand without any vasoconstrictor nerve influence

The calf muscle blood flow and resistance determinations were performed the day after the central hemodynamic investigations and in the ten patients refractory to treatment when blood pressure reduction on minoxidil was considered adequate It was performed in the morning and the patients had taken their antihypertensive medication Initially the arterial circulation was examined by oscillometry (34) No patient showed evidence of large vessel abnormalities The calf muscle flow was recorded with venous occlusion plethysmography using the strain gauge technique (82) The blood pressure was measured indirectly in the arm simultaneously with the flow determinations Initially five readings were made with the patient resting and the resistance at rest was calculated Then arterial occlusion was applied during about 3-4 minutes and the patients exercised the calf by pedalling on a special foot ergonometer until ischemic pain The pedalling time was measured After the arterial occlusion was released five recordings of blood flow were made The highest flow value and the corresponding mean blood pressure was used to calculate resistance at maximal dilatation or minimal resistance (R_{min}) As a rule the mean of three separate determinations was used The ratio between resistance at rest and the resistance at maximal dilatation will be referred to as vascular resting tone considered reflecting the extent of smooth muscle concentration of the resistance vessels in the calf at rest

INVESTIGATIONS DURING MINOXIDIL TREATMENT IN REFRACTORY HYPERTENSION

Study plan

When the ten patients refractory to triple drug treatment we e found to have increased vascular peripheral resistance It was logical to change the vasodilating therapy Consequently hydralazine was discont nued and replaced initially with minoxidil 2 5 mg b i d The doses of the othe drugs (thiazides and propranolol) were kept constant Subsequently the minoxidil dose was increased with 5 mg daily at weekly intervals until

to define in functioning tissue It can be concluded howev r that ische mic work produces an extremely powerf l asodilatation in the calf muscles at present considered close to maximal and expressed as 'maximal blood flow' throughout the present paper

To test the variability of the maximal blood flow det rminations after ischemic work repeated measurements i the twenty patients studied were used The v iation coefficient for three consecutive determination of maximal blood flow was 9 1 % A g adu l inc ease of the consecutive maximal flows we e observed Thus the me ns for the fi st second and third dete mination were 38 5 39 7 and 41 3 ml/100 ml min respectively

Ma imal ha d blood flow

The method u ed for dilatation of the hand ascular bed in the p esent study has p iou ly been discus ed by Si e tsson (67) Thus it was argued that acetylcholine histamine or adenosinet iphosphate gi en into the bra chi l tery could not dil te the hand vessels to the same extent as the method sed It was f rther bs rv d that large doses of norepinephrine gi en i the b achial artery wa complet ly ov ridden by the dilatation procedu e

The iation coefficient fo th ee consec tive determi ations of ma imal blood flow i twenty fou normotensive patients was 6 9 % No t ndency was obse ved towa ds inc sed maximal blood flow with repeated meas eme ts

MEASUREMENT OF VASCULAR RESISTANCE

Calf

The cal l t o of scul re i tance i the calf we based on plethysmo g phi blood flow determination in the calf and simultaneou measu ements of indi ect blood p ssu i the ight rm Du ing st in the compa ison between ef acto y patient and esponde s to the py the indi ect b achial blood p s was athe constant but significa tly increased 111 2 15 4 mm Hg (SD) e compa ed to intr art l l blood pressu e du ing cardiac output det minations 106 6 16 0 mm Hg (x SD) The corr l tion between these blood p essu e measu ement was significant (r n 0** ...

CRITICAL ASPECTS OF THE METHODS

PROCEDURE TO ESTABLISH MAXIMAL VASODILATATION

Maximal calf blood flow

The a curacy and reproducibility in the establishment of maximal vasodila tation is crucial in the study of structural vascular changes suggested to be the reason for increased peripheral resistance in hypertensive patients (24 67) Folkow showed that heating arterial occlusion and muscle work could induce a powerful vasodilator stimulus in the forearm almost maximal after about 5 minutes arterial occlusion (24) Later Conway used arterial occlusion to produce hyperemia but also infused adenosinetriphosphate in to the brachial artery during measurements of blood flow No increase in maximal flow resulting from the infusion was found (9) Furthermore reactive hyperemia has been shown to overcome the effects of intra-venously administered vasoconstrictor drugs (9 24)

Concerning the procedure to produce maximal dilatation of the calf blood vessels it is shown in the present study that 3 4 minutes of arterial occlu ion superimposed by muscle work is a powerful vasodilator stimulus (Tables XI XIV) Considerably large doses of isoproterenol (3 μg/min) given in the femoral artery after the arterial occlusion was released did not increase the vasodilatation produced by arterial occlusion and muscle work alone in another study (39) However the vasoconstriction induced by large doses of norepinephrine (3 μg/min) was not completely overridden by ischemic work Preliminary results with acetylcholine i a indicates that a further increase in vasodilatation after ischemic work might be achieved However the striking skin hyperemia observed indicates that an increased skin blood flow was added to the muscle blood flow

Whether a complete smooth muscle relaxation is achieved during maximal va sodilatation is difficult to prove especially as this entity is difficult

to define in functioning tissue It can be concl ded however that ische mic work produces an extremely powerful vasodilatation in the calf muscles at present considered close to maximal and expressed as 'maximal blood flow' throughout the present pape

To t st the variability of the maximal blood flow determinations after ischemic wo k epeated measurements in the twenty patients studied were used The a iation coefficient for three consecutive determination of maximal blood flow wa 9 1 % A grad l increase of the consecutive maximal flows were observed Thus the means for the first second and third deter mination we e 38 5 39 7 and 41 3 ml/100 ml min respecti ly

Maximal hand blood flow

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The a iation coefficient fo three consecuti e determination of maximal blood flow twenty fou normotensive pati ts wa 6 9 % No tendency was ob ved towa d i creased ma imal blood flow with repeated meas reme ts

MEASUREMENT OF VASCULAR RESISTANCE

Calf

The calcul tion of ascula sistance in the calf wa based on plethysmo- g aphi blood flow det rmination i the calf and simultaneous measureme ts f indi e t blood p ssu in the right arm Du ing rest in the comparison betwe f acto y patient and e ponders to therapy the indi ect brachial blood p s e was the consta t but significantly increased 111 + 15 4 mm Hg (SD) compa d to i t a a te ial blood p e sur du ing ca diac output determination 106 6 16 0 mm Hg (x SD) The co relation between these blood p ess measu ements was ignificant (r 0 85 p 0 001)

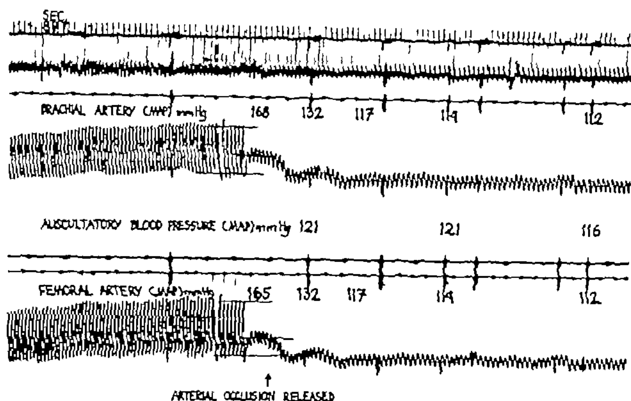


Fig 2 Model experiment showing simultaneously measured auscultatory blood pressure in the right arm and intra arterially recorded pressures in the left brachial (top) and femoral (bottom) artery during ischemia and after the arterial occlusion was released (arrow)

It might be questioned whether the blood pressure in the arm is representative for the blood pressure in the leg during maximal vasodilatation in the calf In order to establish the relation of indirect blood pressure in the arm to intra arterial recordings of blood pressure in the brachial and femoral arteries a model experiment was performed In four patients with resting blood pressure varying within a wide range catheters were inserted in the brachial and femoral arteries Simultaneous auscultatory blood pressure in the arm was then compared to intra arterial pressures during the usual experimental conditions to produce maximal vasodilatation in the calf A curve from this model experiment on one patient representative also for the other three patients is illustrated in Fig 2

Intra arterially measured blood pressure simultaneous in the brachial and [illegible] close resemblance The indirect blood pressure showed

Table III Model experiment in four patients showing results from simultaneously measured auscultatory blood pressure in the right arm and int a arterially recorded pressures in the brachial and femo al arteries In the meas rements withi 10 seconds desufflation of the blood pressure cuff was started at the moment of arterial occl sion release In the measu ements 10 15 seconds afterrelease of arterial occlusion the blood pressure cuff was insufflated immediately after arterial occl sion r lease

P tient	Blood pressure (MAP) mm Hg with in 10 sec after r lease or arterial occlusion			Blood pressure (MAP) mm Hg 10 15 sec after release of arterial occlu ion		
	Auscul t tory	I a b achial	I a femoral	Auscul tatory	I a brachial	I a femoral
1	121	132	132	124	118	119
2	129	121	114	123	117	125
3	135	151	147	130	133	134
4	116	108	117	114	114	114

less good ag eement when directly recorded especially within 10 seconds fte release of the a terial occlu ion i the leg It was also obser ed that immediat ly afte the arterial occlusion was released a r pid blood p essur redu tion took place i both a teries (Fig 2) This blood pres su e reduction occ red du ing bout 5 second and s bsequently slower blood p ss e reduction was observed during 30 60 seconds when the blood p ess re i the femo l d brachial rteries was educed towards esting alues When dir ct and i direct blood p ss res were compared 10 15 se cond aft lease of the rterial occlusion better ag eement was ob served (Table III)

It is obviou that the esi tance calculated from blood flow and blood p essu e might be biased if the indi ect blood p essure in the arm is measur d du ing the pha e of rapid reduction However this could not be the cas i the p ent study on patients refractory (Group A) and re ponding to the apy (Group B) since the blood p ssure simultaneous with the ma imal flow d termination was not measured earlie than 10 second fte the el ase of the arterial occlusion when the blood p essu e in the b achial nd femo al artery was elatively stable A systematic equally large ro in indi

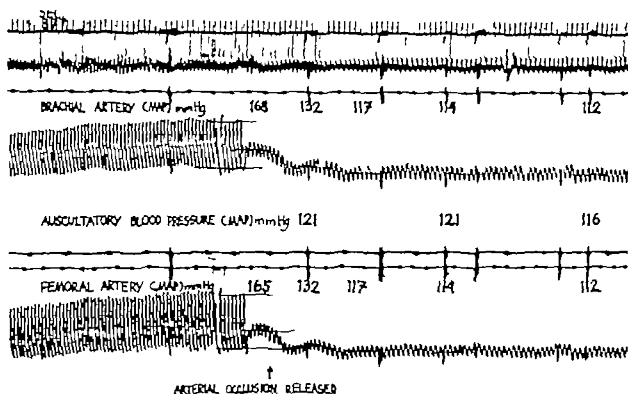


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Intra arterially measured blood pressure simultaneous in the brachial a d femoral artery showed close resemblance The indirect blood pressure showed

cardiac output determinations and during hand blood flow determinations at rest (r = 0 75 p 0 001)

To test the variability of the blood flow resistance in the hand at maxi mal asodilatation three consecutive determinations on twenty-four normo tensi e patients were used The riation coefficient was 6 8 % No syste matic change in r sistance was observed in the consecutive ecordings

both patient groups in this study The correlation was good (r = 0 88) (Fig 3) Consequently the error of the indirect blood pressure measurements should affect all patients equally and the resistance of vascular blood flow in the calf should be equally over estimated in both groups

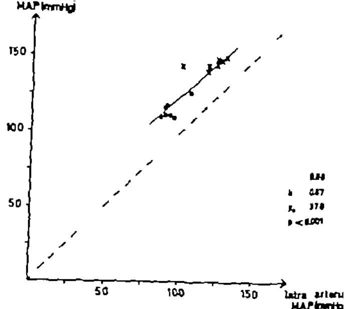


Fig 3 Correlation between simultaneously measured intra arterial and auscultatory blood pressures x = patients refractory to treatment o = patients responding to treatment

To test the variability of the blood flow resistance during maximal vasodilatation in the calf three consecutive determinations in the twenty patients studied were used The variation coefficient was 9 7 % No systematic change in resistance was observed in the consecutive recordings

Hand

In the present series of twenty patients calculations of vascular resistance in the hand was based on plethysmographic blood flow determinations and simultaneous intra arterial blood pressure recordings in the contra lateral brachial artery The patients had both hands in water plethysmographs During maximal flow experiments the same temperature (43° C) and arterial occlusion time were applicated bilaterally The patients were instructed to exercise both hands simultaneously Consequently after these procedures the blood pressure during hyperemic flow would be equally affected in both brachial arteries The moments for blood flow determinations were marked on the blood pressure curves to ensure simultaneous recordings The intra arterial mean blood pressure during cardiac output determinations was 106 6 + 16 0 mm Hg (x + SD) in the twenty patients studied and during hand blood flow determinations at rest 106 8 + 14 3 mm Hg (x + SD) There was a significant correlation between mean arterial pressure during

another ten patients arious renoparenchymal di eases were found Reno vasc lar hypertension was found in fou patients Seven cases of unilate al hyd onephrosi were detected In addition there was one case of aortic coarctation one of p imary aldosteronism and t o of primary hyperpa athy roidism I 29/40 (73 %) cases the diagnosis was made from the patient s history I two case did the investigations lead to u gical interaction

BLOOD PRESSURE REDUCTION (P per II)

F g 4 pr se ts the distribution of blood press re I treated and untrea ted patie ts at the sc e ing examination at the thi d visit to the hy pe te sion cli I and aft r on (n=646) and two year (n=624) treatment The d s r pancy i umbe was caused by patients who were lost to follow up The dist but ons of ystolic blood pressur s and diastolic blood p es e initi lly and ft one and two years t atment we e g adually shifted to the l ft The propo t on of patients with systolic blood pr su e o dia tol c blood p e es above 160 o 95 mm Hg decreased signi ficantly from 68 (SBP) and 84 > (DBP) initi lly at the hypertension cli ic to 33 (SBP) and 5 (DBP) aft two years treatment Co r sponding ly the p opo t on f subjects with systolic blood p essu es above 170 or di tolic blood p s abo e 105 mm Hg dec ea ed from 47 % (SBP) and 53 (DBP) t 17 (SBP) and 17 (DBP) The a e age blood p essu lso dec eased from 169/106 mm Hg initially to 153/96 mm Hg after two ye rs tre tment

When o ly pa ts on d ug t eatme t at the second annual examination we e ncluded (n=389) the e wa sig ifica t reduction of sy t lic (15 mm Hg) and d a tol blood p ssur (10 mm Hg) du ing two years follow-up (T bl V) The majo p t of the eduction was achieved d ing the first ye

Du ing the thi d yea f follow-up the blood p essu control was studied he 108 pat e t w th diastoli blood pre su e exceeding 105 mm Hg at he s ond annual xam nation In 51/108 (47 %) patients a blood p essure below 95 mm Hg was achieved (T bl VI) In 33/108 patients (30 %) the ade quat cont ol was achi ed fto changes (inc easing doses or additional d ug) ther py but in 18/108 (17 %) no change in therapy was needed I 5 108 (3 %) patients the blood pressu e control was inadequate

RESULTS

PREVALENCE OF HYPERTENSION (Paper I)

Of the 7455 men who were examined at the screening 1159 (16 %) had blood pressures above 175 mm Hg (SBP) or 115 mm Hg (DBP) or both or were re ceiving antihypertensive treatment After exclusion of patients with blood pressure below the cut off points at the re examination 835 (11 2 %) were considered hypertensive and referred to follow-up (Table I)

PREVALENCE OF SECONDARY HYPERTENSION (Paper I)

Of the 686 patients investigated at the hypertension clinic 40 patients (5 8 %) were shown or suspected to have a specific cause of hypertension (Table IV) Fifteen patients had chronic glomerulonephritis and in

Table IV The frequency of diseases possibly causing secondary hypertension (n=686)

	n	%
Renoparenchymal disease	25	3 5
Chronic glomerulonephritis	15	
Renal tuberculosis	4	
Gouty nephropathy	3	
Renal dysplasia	2	
Analgesic nephropathy	1	
Renovascular disease	4	0 6
Aortic coarctation	1	
Primary aldosteronism	1	
Primary hyperparathyroidism	2	
Unilateral hydronephrosis	7	1 0
Total	40	5 8

ble V Mea s ( ) and standard deviations (Sx) of systolic (SBP) nd di stolic blood pressur (DBP) at scr ening initially at the hypertension clinic and after one and two years tre tment Only patients followed du ing the whole observation period and with antihypertensi e therapy are included (n 589)

	SBP		DBP	
	x	Sx	x	Sx
t sc eening	184	19 1	114	12 0
nitially at the cli ic	168	20 1	106	12 4
ft one yea	158	18 2	97	9 8
fter two years	153	17 7	96	9 8

'able VI Blood p s re cont ol (diastoli blood p essu _95 mm Hg) d ring the thi d yea I patients with diastolic blood pressur exceeding 105 mm Hg at the second annual examination (n = 108)

	No	%
Adequate blood pre ur o t ol ft the apy change	33	30
Adequat blood pres co trol without the apy chang	18	17
Inadequate blood p e control	25	23
Ref acto y to t eatme t	20	19
Lost to follow-up	8	7
Dead	4	4

n pit of dose increase o effo ts to find s itable drug combinations gene ally bec se the pati t could not tole ate the medication or showed poo coope bil ty I 20/108 (19 %) patients conside ed adequately me dic t d with th e d ug o mo and showing good cooperability the blood p su control was till poor Eight patient in this group we e I t to f the follow-up and fou patients died during the thi d year

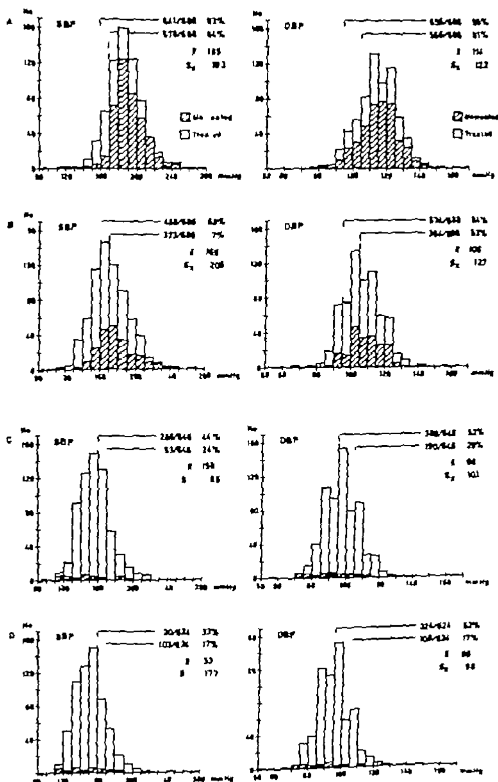


Fig 4 Systolic and diastolic blood pressure distribution for t eated and untreated patients at screening (A) initially at the hyper tension clinic (B) and after one (C) and two years treatment (D) Means and standard deviations are also given as well as the f e quency of patients exceeding 160 and 170 mm Hg (SBP) and 95 and 105 mm Hg (DBP) respectively

Seventeen patients (17/473 = 4 %) had to discontinue β adrenergic blocking treatment during the first year In five patients this was due to ivid dreams or insomnia Pulmonary obstructive symptoms were the easons in four patients and gastrointestinal symptoms in another two One patient developed bradycardia and another experienced worsened symptoms f om in termittent claudication Four patients had unspecific symptoms and wanted to change the β receptor blocking drug

Two patients developed symptoms of arthritis while on hydr lazine but none had a true SLE like syndrome with positive titres for antinuclear factor

In 34 patients during the fi st yea the side-effects causing withdrawal we e caused by other dr gs The numbe of patients on each drug was how-ev too low to mak rational analy is meaningful

During the second yea nine patients (9/319 = 3 %) on diur tics and six pati ts (6/484 1 %) on β ad ene gic blocking d ugs had to discontinue tr atment (Table VII)

PATIENT ADHERENCE

Twe ty- ine patients (4 2 %) ref sed to pa ticipate or we e lost to follow-up without known eason (Table VIII) Another 33 patients (4 8 %) were not followed du ing the enti e obse v tion pe iod of two yea s Eleven patients p f ed t eatment by othe phy icians eleven left the city and eleven di d

T bl VIII Numbe of pati ts and reasons for d op-out d ing two yea s t the hyperte sion clinic (n 686)

	Fi st year No	%	Second year No	%
Ref sed/unknown e son	18	2 6	11	1 6
P f ed t atment by othe physicians	9		2	
Moved	7		4	
Died	6		5	
Tot l	40	5 8	22	3 2

In 90/610 (15 %) patients during the first year and in 15/589 (3 %) patients during the second year an antihypertensive agent had to be discontinued because of adverse effects considered caused by the drug In another twelve cases (eight during the first and four during the second year) the relationship between the drugs and the adverse effects was considered improbable These twelve cases were not included in the analysis below

The reason for withdrawal concerning the three antihypertensive agents most commonly used during the first and second year are listed in Table VII During the first year thirty seven patients (37/312 = 12 %) had to discontinue their diuretic treatment Low levels of S-potassium in spite of potassium supplement was the most common reason Seven patients developed S urate levels exceeding 500 mmol/l and one patient developed clinically overt gout considered secondary to the diuretic treatment Four patients had to discontinue the treatment because of gastrointestinal symptoms and four developed clinically overt diabetes mellitus with glucosuria Three patients complained of unspecific symptoms and wanted to change the diuretic drug

Table VII Frequency of adverse effects causing withdrawal of the drug during the first and second year of treatment

	First year No	%	Second year No	%
Diuretics	37/312	12	9/319	3
Diabetes mellitus	4		1	
Gastrointestinal symptoms	4	4	1	1
Gouty arthritis	1		2	
Others	3			
S potassium < 3 4 mmol/l	18	8	4	2
S urate > 500 mmol/l	7		1	
β adrenergic blocking drugs	17/473	4	6/484	1
Sleep disturbances	5		3	
Pulmonal obstructive symptoms	4		1	
Gastrointestinal symptoms	2		1	
Bradycardia	1		1	
Intermittent claudication	1			
Others	4			
Hydralazine	2/207	1	0/225	0
Arthritis	2		0	

Central hemodynamic investig tions

As illustrated in Table X the mean intra arterially recorded blood pres sur differed significantly between refractory patients and the respon ders (p 0 001) The cardiac index heart rate and stroke volume index did not differ between the groups Consequently total peripheral resist nce index in the efractory hype tensive patients was significantly increased (p 0 05)

Regional asc la r si tance

The results from the blood flow determinations in the calf are shown in Table XI The a rage blood flow at r st was similar in refractory a d responding pat ents b t the re istance at est was significantly i c e sed i the ef acto y group (p 0 01) After a terial occlusion and muscle workthe flow inc ased 15 fold but the e was no diffe ence between the group i thi respe t The cal lat d e istance t maximal dilatation (R_{ml}) howe er was ignifica tly inc sed i the fracto y patients (p 0 05) No diffe enc betwe the groups concerning v scular ton at est (R_{est}/R_{ml}) was found The e wa a stati tically significant corre lation between t tal pe iphe l e i tanc i d c lcul ted f om cardiac output and mea a te ial blood p e e and blood flow resistanc at rest (0 56; p 0 01) (Fig 5)

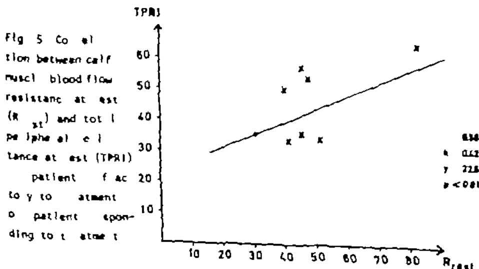


Fig 5 Co el tion between calf muscl blood flow resistanc at est (R_{st}) and tot l pe iphe al e i tance at est (TPRI)
patient f ac to y to atment
o patient spon- ding to t atme t

HEMODYNAMIC CHARACTERISTICS IN PATIENTS REFRACTORY TO TRIPLE DRUG TREATMENT (Paper III)

Plasma volume

The hematocrites did not differ between refractory patients and responders and consequently differences in total blood volume were reflected by the plasma volume (Table IX) There was no significant difference between the groups either concerning total plasma volume or plasma volume per cm body height but the refractory patients tended to have slightly higher values Furthermore no significant correlation was found between plasma volume per cm body height and indirect mean arterial blood pressure (r = 0 36 n s) or intra arterially recorded mean arterial blood pressure (r = 0 42 n s)

Table IX Total plasma volume and plasma volume per cm height in refractory patients (Group A) and patients responding to therapy (Group B)

Patients		Plasma volume (l)		Plasma volume (ml/cm)	
		A	B	A	B
KR	AN	3 7	2 8	21 4	15 6
KEW	SG	3 1	2 7	17 8	15 4
KES	SH	3 1	3 7	18 0	20 7
LW	TB	4 8	2 4	26 8	14 0
EL	HA	2 6	2	14 8	12 6
EE	OR	3 6	3 1	20 7	17 7
BN	BGH	3 6	4 0	20 2	21 7
OK	DE	3 5	3 2	19 6	18 9
EA	SW	3 4	2 9	19 2	16 4
RS	EG	3 3	3 0	19 0	17 1
Mean		3 47	3 00	19 75	17 01
SD		0 57	0 55	3 09	2 85
Significance		ns		ns	

Cent al hemodynamic inve tigations

As illust ated in Table X the mean intr arteri lly recorded blood pres sure differed signific ntly between refractory patients and the espon ders (p 0 001) The cardi c index heart rate and stroke volume index did not differ between the groups Consequently total peripheral resistance index in the ref actory hypertensi e patients was significantly increased (p 0 05)

Regional asc la r sistance

The result from the blood flow determinations i the calf are shown in Table XI The a e age blood flow at r st was similar in refractory and sponding pat ent but the e istanc at est was ignificantly increa sed i the refracto y group (p 0 01) Afte a teri l occlusion and muscle work the flow increased 15 fold but the a we no diff rence between the groups i this respect The calc lated esistance at maximal dilatation (R_{ml}) howeve was significantly inc eased in the efractory patient (p 0 05) No diffe ence betwee the g oups conc rning ascular tone at rest (R_{st}/R_{min}) we found There wa a tatistically significant corre-lation between total periphe l resistance index calc lated f om ca diac output and mea a te ial blood pressure and blood flow esistance t rest (0 56 p 0 01) (Fig 5)

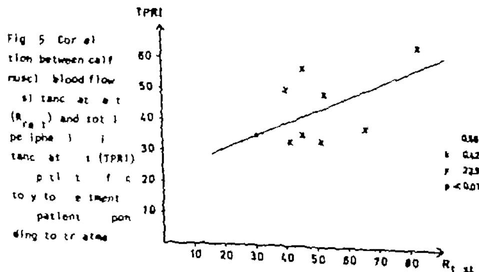


Fig 5 Cor el tion between calf muscl blood flow si tanc at e t ($R_{re\ t}$) and tot l pe iphe l i tanc at i (TPRI) p ti t f c to y to e tment patient pon ding to tr atme

HEMODYNAMIC CHARACTERISTICS IN PATIENTS REFRACTORY TO TRIPLE DRUG TREATMENT (Paper III)

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Table IX Total plasma volume and plasma volume per cm height in refractory patients (Group A) and patients responding to therapy (Group B)

Patients		Plasma volume (l)		Plasma volume (ml/cm)	
		A	B	A	B
KR	AN	3 7	2 8	21 4	15 6
KEW	SG	3 1	2 7	17 8	15 4
KES	SM	3 1	3 7	18 0	20 7
LW	TB	4 8	2 4	26 8	14 0
EL	HA	2 6	2	14 8	12 6
EE	OR	3 6	3 1	20 7	17 7
BN	BGH	3 6	4 0	20 2	21 7
OK	DE	3 5	3 2	19 6	18 9
EA	SW	3 4	2 9	19 2	16 4
RS	EG	3 3	3 0	19 0	17 1
Mean		3 47	3 00	19 75	17 01
SD		0 57	0 55	3 09	2 85
Significance		ns		ns	

T bl XI Re ng blood flow nd l t co and ma imal blood flow and lst nce wall
t ng ton the lf mu l sc l bed l patl t f ct y (G oup A) and
pond ng (G oup B) t t pl drug t tme t

P tlent		R ting flow ml/100 ml ml		Re ting sistan (R st) PRU_{100}		Maximal flow ml/100 ml ml		Re istance at maximal flow (R_{min}) PRU_{100}		Resting ton (R_{rest}/R_{min})	
A	B	A	B	A	B	A	B	A	B	A	B
KR	AN	2 8	1 6	47 3	54 8	33 3	46 4	4 6	2 8	10 3	19 6
KEW	SG	3 1	2 9	44 9	34 1	41 6	48 2	3 3	2 3	13 6	14 8
KES	SH	2 7	3 3	45 0	29 5	39 0	44 2	4 1	2 4	11 0	12 3
LW	TB	3 0	4 0	39 4	23 8	37 1	31 6	3 7	3 0	10 6	7 9
EL	HA	1 6	3 1	81 3	31 3	27 7	30 5	5 0	3 3	16 3	9 5
EE	OR	2 4	2 4	52 1	41 0	52 2	38 3	2 4	2 7	21 7	15 2
BN	BGH	3 2	2 8	40 8	34 3	44 0	38 5	3 1	2 7	13 2	12 7
OK	DE	2 5	3 5	46 8	30 0	39 5	36 6	3 1	2 5	15 1	12 0
EA	SW	1 8	2 1	65 2	48 8	41 9	45 7	3 0	2 3	21 7	21 2
RS	EG	2 4	2 7	50 1	35 8	32 4	29 0	3 5	3 5	14 3	10 2
Means		2 6	2 8	51 3	36 3	39 0	38 9	3 6	2 8	14 8	13 5
SD		0 5	0 7	12 8	9 4	6 9	7 0	0 8	0 4	4 1	4 3
Significance		s		p 0 01		ns		p < 0 05		ns	

Table X Intra arterially recorded mean arterial pressure (MAP) cardiac index (CI) heart rate (HR) stroke volume index (SVI) and calculated total peripheral resistance index (TPRI) in refractory patients (Group A) and patients responding to triple drug therapy (Group B)

Patients		MAP mm Hg		CI (l/min m^2)		HR (beats/min)		SVI (ml/m^2)		TPRI (U/m^2)	
A	B	A	B	A	B	A	B	A	B	A	B
KR	AH	118	92	2 4	2 2	59	61	41	36	48 2	41 8
KEW	SG	130	100	2 3	2 3	58	59	40	39	56 5	43 5
KES	SH	124	106	3 5	3 7	55	58	64	64	35 4	28 6
LW	TB	124	86	2 5	2 8	67	67	37	42	49 6	30 7
EL	HA	127	86	2 0	2 1	54	58	37	36	63 5	41 0
EE	OR	111	106	2 3	2 4	74	48	31	50	48 3	44 2
BH	BGH	136	89	4 1	3 0	88	65	47	46	33 2	29 7
OK	OE	106	95	2 0	2 7	60	50	33	54	53 0	35 2
EA	SW	117	90	3 1	3 0	50	56	62	54	37 7	30 0
RS	EG	100	89	3 0	2 8	63	65	40	43	33 3	31 7
Mean		119	94	2 72	2 70	63	59	44	46	45 9	35 6
SD		11 2	7 6	0 7	0 5	11 2	6 3	11 4	9 1	10 5	6 3
Significance		p 0 001		ns		ns		ns		p 0 05	

Tabl XII Sympathoplegic blood flow and si ta nd maximal blood flow nd ist nc as woll a ympathopl g c tone of the hand vessel) patients ref actory (G oup A) nd r ponding (G oup B) t t iple d ug tr atment

Pati t		Sympathopleg flow ml/100 l m		Sympathopl gic l ta ce (R_{ymp}) PRU_{100}		Maximal flow ml/100 ml ml		Re istance at maximal flow (R_{min}) PRU_{100}		Symp thoplegic tone (R_{symp}/R_{ml})	
A	B	A	B	A	B	A	B	A	B	A	B
KR	AM	9 4	13 4	13 1	6 7	35 2	45 6	4 2	2 5	3 1	2 7
KEW	SG	9 8	13 7	14 3	8 3	30 0	39 3	5 4	2 8	2 6	3 0
KES	SH	13 2	10 6	7 7	10 2	28 9	38 1	3 8	2 7	2 0	3 8
LW	TB	10 0	9 1	12 7	9 9	34 5	30 4	3 7	2 7	3 4	3 7
EL	HA	8 5	16 6	15 4	5 0	26 7	26 3	5 7	3 1	2 7	1 6
EE	OR	7 5	13 2	14 2	7 8	29 4	28 4	4 6	3 8	3 1	2 1
BN	BGH	14 6	18 0	7 4	5 0	48 6	47 5	2 7	2 0	2 7	2 5
OK	DE	13 2	14 1	7 9	7 0	43 0	39 8	2 5	2 4	3 2	2 9
EA	SW	13 9	15 9	6 6	6 1	35 1	27 9	3 9	3 2	1 9	1 9
RS	EG	13 9	8 0	6 2	11 9	39 8	28 7	2 3	3 3	2 5	3 6
Mean		11 40	13 3	10 6	7 8	35 10	35 20	3 9	2 9	2 7	2 8
SD		2 6	3 2	3 7	2 3	6 9	7 8	1 2	0 5	0 5	0 8
Significance		ns		ns		ns		$p < 0\ 05$		ns	

The results from the determinations of hand blood flow are shown in Table XII There was no difference at rest between the refractory patients and the responders as far as blood flow was concerned Neither was there any significant difference between the groups concerning vascular resistance but it tended to be higher in the refractory patients During maximal va sodilatation blood flow was almost identical in refractory and responding hypertensives The resistance at maximal dilatation showed a significant increase in the refractory group ($p < 0\ 05$) compared to the responders No difference was found concerning vascular tone The correlation between total peripheral resistance and sympathoplegic resistance in the hand was statistically significant ($r = 0\ 63$ $p < 0\ 01$) (Fig 6)

The ratio between treated mean arterial blood pressure for the two groups of patients (145 115 = 1 3) was almost the same as the ratio be tween resistance at maximal dilatation in the calf (3 4 2 8 = 1 2) and resistance at maximal dilatation in the hand vessels (3 9 2 9 = 1 3) as well as total peripheral resistance index (46 0 35 6 = 1 3)

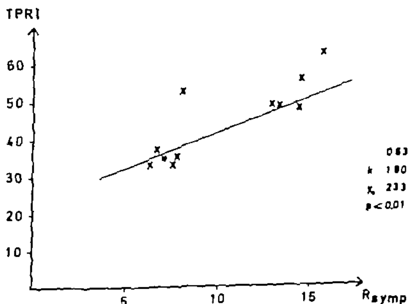


Fig 6 Correlation between sympathoplegic hand blood flow resistance (R_{symp}) and total peripheral resistance at rest (TPRI)
x = patients refractory to treatment o = patients esponding to treatment

Regional vascular eslstanc

The average blood flow in the calf at rest was significantly increased when the patie ts had minoxidil treatment (p 0 001) nd since the blood pressure dec e sed the calcul ted ascular resistance at rest was edu ced (p 0 001) (Table XIV) After rterl l occl sion and muscle wo k the blood flow was increased to the same ext nt befo e and d ring mino idil treatment The e was no change in resistanc at maximal dilatation hen the patients had minoxidil compared to when they we e treated with hydra lazine The e was a significant cor el tion between the blood p essure eduction and the change in esting blood flow (= 0 66; p 0 05) (Fig 7) The e was no co r l tion betwee the blood p e su e eduction and change i resting esistance (r 0 47 s)

Adve eff t

One of the patients (BM) developed mild ankle oedema when recei ing 20 mg daily f minoxidil This ign disappea d when f rosemide 40 mg daily was added to the t ipl drug t eatme t Eight patients had mild hypertrichosis of the f ce t unk and rms No patient had we ght gai o com-pl ined of ymptoms f any k nd No abnormal changes f om p et e t ment levels of S t ansaminase S lect olyt o S eati ine we e obse d No t hyca di wa noted No pa i t wanted the drug to be discontinued whe off d thi opt on

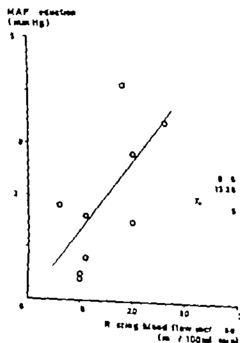


Fig 7 C l t on betwe blood p reduc tion and muscl blood flow inc ea e d ing mino d l t atme t

Blood pressure reduction

After 4 8 weeks on increasing doses of minoxidil all patients had a blood pressure reduction at the clinic considered adequate All patients had blood pressures below 170/100 mm Hg and the mean arterial blood pressure reduction was 39 mm Hg ($p < 0$ 001) when compared to pretreatment blood pressure The reduction was 31 mm Hg ($p < 0$ 001) when compared to blood pressure on triple drug treatment with hydralazine as the vasodilating agent No significant change in heart rate was noted when the patients had minoxidil instead of hydralazine (Paper IV)

Plasma volume

The hematocrites did not differ between the examinations when the patients were on hydralazine or minoxidil Consequently differences in blood volume were reflected by plasma volume There was no change in total plasma volume or plasma volume per cm body height before and during minoxidil treatment (Table XIII) Furthermore no correlation was found between the change in blood pressure and the change in total plasma volume per cm body height

Table XIII Total plasma volume and plasma volume per cm body height before (B) and during (D) minoxidil treatment

Patients	Plasma volume (l)		Plasma volume (ml/cm)	
	B	D	B	D
KR	3 7	4 1	21 4	23 7
KEW	3 1	3 6	17 8	20 7
KES	3 1	3 6	18 0	20 9
LW	4 8	3 9	26 8	1 8
EL	2 6	3 4	14 8	19 4
EE	3 6	4 5	20 7	25 9
BN	3 6	4 0	20 2	22 5
OK	3 5	3 6	19 6	20 1
EA	3 4	3 5	19 2	19 8
RS	3 3	3 3	19 0	19 0
Mean	3 47	3 75	19 8	21 4
SD	0 57	0 36	3 09	2 15
p	ns		ns	

GENERAL DISCUSSION

THE SCREENING EXAMINATION

The patients l the pr sent st dy were de l ed from the screening of a random third of the male population aged 47 54 The patient series was in tended to be unselected and ep se tati e for the middle aged male hyper tensive population Selection occur ed however al eady in the screening phase as 25 % of the invited subjects did not attend This group has been shown to have a high mortality ate i diseases not associated with hy pertension (88) Of the patients conside ed hypo tensi at the sc eening examination 18 % declined further follow up (Table I) Although it is con cei able that a large part of these patients were followed by other physicians a conside able number of patients could not be examined in the p sent study thus limiting the pos b lity to gene alize the results Howeve the p esent patient ie is con ide ed to repre e t the total male middle-aged hypo t n ive popul tion i fa bette manne than hos pital se ies do The participat on ate i the p esent study i comparable to that in most other studi s of this kind

The cut off poi ts fo hype t s on at the c ening examination may seem high Howeve the a bitra y blood p essu le ls were chosen to identi fy the patie ts i the uppe dece til of the blood p es u e dist ibution F thermore a high frequency of hype tens o g invol ement has been demonst ted i patients exceeding these l els (76) i a subsample of the p esent patient mat rial the blood p o su level of 175/115 mm Hg in the afte noon corresponded to 162/101 mm Hg whe me s ed i the mor ing (86) which is cl se to the WHO r commendations (83)

THE HYPERTENSION CLINIC

O ganiz tion

The new ttitude concerning man geme t of hype t sion implies identifica tion of all pati ts at isk standa diz d diagnosic wo k-up and the apy

Table XIV Resting blood flow and resistance (R_{rest}) blood flow and resistance at maximal dilatation (R_{min}) and resting tone before (B) and during (D) minoxidil treatment

Patients	Resting flow ml/100 ml min		Resting resistance (R_{rest}) PRU_{100}		Maximal flow ml/100 ml min		Resistance at maximal dilatation (R_{min}) PRU_{100}		Resting tone (R_{rest})/(R_{min})	
	B	D	B	D	B	D	B	D	B	D
KR	2 8	4 1	47 3	28 0	33 3	31 0	4 6	4 2	10 3	6 7
KEW	3 1	4 9	44 9	24 3	41 6	34 6	3 3	3 7	13 6	6 6
KES	2 7	4 7	45 0	23 6	39 0	46 3	4 1	2 5	11 0	9 4
LW	3 0	5 6	39 4	17 9	37 1	46 3	3 7	2 6	10 6	6 9
EL	1 6	2 6	81 3	51 5	27 7	25 0	5 0	5 7	16 3	9 0
EE	2 4	3 4	52 1	32 9	52 2	40 0	2 4	2 8	19 3	11 8
BN	3 2	5 2	40 8	21 1	44 8	39 0	3 1	4 5	13 2	4 7
OK	2 5	3 6	46 8	34 7	39 5	33 0	3 1	3 7	15 1	9 4
EA	1 8	2 4	65 2	41 3	41 9	38 1	3 0	2 8	21 7	14 8
RS	2 4	3 5	50 1	34 9	32 4	30 7	3 5	3 0	14 3	11 6
mean	2 6	4 0	51 3	31 03	39 0	36 4	3 58	3 55	14 5	9 1
SD	0 52	1 08	12 75	10 19	6 90	6 87	0 79	1 02	3 7	3 0
Significance	p 0 001		p 0 001		ns		ns		p < 0 001	

blood pr ssure measurements ha e been made but still a biologic varia tion as well as inter-obse ve and intra-observer variations can be expected

I the patient series described (n=686) the blood pressure measurements have been done t different times of the day (8 a m 4 p m) This would imply that a patient could be examined at 8 o clock at one visit and at 3 o clock at another However the annual blood pressure measu ements used for comparisons were done in associ tion with a visit to the physician and at fairly the same time of the day each year Minor en ironmental factors affecting the result a e difficult to void during clinical circumst nces There is no r ason to believe however that such environme tal fluctua tions would result in bette l o lower blood p su e res lts

Ideally the same nurse should examine the same patient on e ery occasion but for practical reasons this has been impossible Co s quently an inter-observer va iation must be p ese t This variation however is con sidered mino as j dged from int -observe diffe enc s from imultaneous measurements pe formed The same th ee nu se constit ted the staff du ing the observation period Repeated blood p ess r measurements by the same observe s lso how good eprod cibility

Blood pr s r control

The eduction of sy toli and dia tolic blood pressure between sc eening and the i tial meas eme ts t the hype t sion cli ic (Table V) was anticipated fo se eral eason F tly a con ider ble propo tion of patient were al ady i the i itial phase of antihype te sive t e tment on thei third isit to the cli i Se ondly it is well known that the blood p essu e g adually dec ease without therapy du ing epeated mea su eme ts (17) Thi dly methodological diff rences such as time of the day and po tu e and a tati tical phenomenon like gression towa ds the mean might explai some of the eduction With the first f t in mind the blood p e s duction achieved du ing the fi t year might be con- t de d unde timated but i nonethel ss mainly a result of the antihy pe ten ive drug t eatme t Afte anothe yea thes blood p s u e le l we mai ta ned eve educed somewhat The esults reg rding blood p ssu e eduction du ing the fi t two yea s we e not tl ely positi e Afte the second y 52 % of the patient till had a di stoli blood

and a responsibility for a continuous follow-up *In that* sense the out patient hypertension clinic in the present study could be regarded as a model for the management of *large scale* hypertensive populations This is possible only if nurses replace *the physicians* in several functions and it a standardized form for diagnostic work-up is followed Thus the physician has the results *from three blood pressure* measurements and the data *from* the diagnostic work up at hand at his first appointment with the patient a rational and time saving approach After the initial phase of *treatment* the nurses have the responsibility for blood pressure check ups and advice to the patients regarding the therapy and possible side *effects* This function is supervised by the *physician*

It might be anticipated that the patients could *feel repelled in an organization* characterized by effectiveness and swiftness as described here However the results *concerning patient* adherence contradict thi assumption

The initial experiences from the hypertension clinic leads to the conclu*sion* that a team of one full time nurse one part time secretary and one full-time or a few part-time physicians can cope with the management of about 500 hypertensive patients of the kind studied here

It must be remembered that the problem of treatment of hypertension cannot be solved by out patient hypertension clinics of the kind described here The prevalence of hypertension is so high that the majority of patients must be managed by general physicians However the methods used are simple and could probably have wider applicability

Blood pressure measurements

The blood pressure in all individuals is known to fluctuate with n a wide range A considerable difference of the blood pressure level d i g sleep and during different daily activities as well as a rapid ise in blood pressure from certain stimuli like pain fear and excitement is descr bed (60 a) Consequently the great variability of the blood p ess e s often a problem in the diagnosis of hypertension

In the present study serious attempts to standardize the procedure of

other studies (1 2 31) especially as only 4 4 d ring the two yea s follow-up were true fallu es to comply (Table VIII) Low cost for medical services and drugs easy accessability to nurses and physicians and the fa t that the clinic activ ly located and arranged new appointments for patient who failed to attend at scheduled visits are considered the main re sons for this encouraging result

PREVALENCE OF SECONDARY HYPERTENSION

The p evalence of seconda y hype te sion was low (5 8 %) and that of sur gically curable cases e e lower The p evalence of secondary hypert nsion i this st dy was lower than othe timates (18 22 33) The analysis is however the first one to be done i subjects de ived from sc eening a total population F thermo only men aged 47 54 years were studied The p evalence of secondary hypertension might be highe in women or in young r men The esults ugg st howeve that in middle aged men exten sive investigations aimed t detecting secondary hypertension a e not ne cessary in those found to have hype t nsion at sc eening I patients with hyperten ion efer ed to hospitals secondary hype tension is probably ove rep se ted and more e tensiv routine investigations might be justi fied Renog aphy s scr ning i strument fo enovascular hype tension cannot be ecommended The p alence of renovascular hypertension was low and the we e many false-positive renog ams (3) The esults suppo t the findings of cent cost benefit analy es of u og aphy a d enog phy as s eening i st ume ts fo eno ascula hype tension (54) and of compa isons of gical and medi al t e tme t of eno ascula hype ten ion (55) The tests sed led to su gery fo two patients either of whom was ur d The pr sent sults and those quoted above thus suggest that in planning fo community cont l of hype ten ion secondary hype ten ion should not be sought with ad anc d i vestigati e methods Instead only patients whose h sto y physical st tus o outine test res lts suggest secondary hype tension should be s bmitt d to f the i vestigations The remainda more than 95 % hould be given d ug t atment

HEMODYNAMIC CHARACTERISTICS IN PATIENTS REFRACTORY TO TREATMENT

It has be hown fo eve al antihype tensive drugs that esistance to hypoten ive t tme t i ssoci ted with sodium r te tion and expanded

pressure exceeding 95 mm Hg which was the therapeutic goal (Fig 4) However acceptable control e g diastolic blood pressure below 105 mm Hg was achieved in 83 % of the patients at the second annual examination

The results of blood pressure control during the third year in the group with diastolic blood pressure above 105 mm Hg indicate that in certain patients (Table VI) the blood pressure elevation at the second annual exa mination was only a temporary increase at this visit as a substantial reduction was observed without increment of the treatment Furthermore improved blood pressure control was achieved after dose increments in a minor group of patients also during the third year of follow-up Thus even in an unselected hypertensive population treated by physicians with a special interest in hypertension a long period of treatment was often needed to achieve adequate blood pressure control

Adverse drug effects

The frequency of side effects causing withdrawal of a drug during two years treatment must be considered acceptable In spite of this the frequency of adverse effects during the first year emphasizes the need for frequent appointments with a nurse or a physician and a possibility of telephone contact in the early phase of antihypertensive treatment On the other hand fewer side effects were registered during the second year of treatment indicating that less close supervision is necessary after the initial treatment phase

The β adrenergic adrenoreceptor blocking drugs caused fewer adverse effects than the diuretics (Table VII) This might however be due to the fact that diuretics were more often prescribed to patients with advanced hyper tensive disease in whom a higher frequency of side effects per se might be anticipated Furthermore the frequency of adverse effects with diure tics would also have been considerably reduced if a somewhat lower level of S potassium had been accepted

Patient adherence

The drop out rate at the hypertension clinic 6 % during the first year and 3 % during the second can be considered low in comparison with

asomotor blockade (sympathoplegic tone Table XII) The higher vascular resistance in the refractory group can therefore hardly be explained by an increased ascular smooth muscle tone

The other possible explanation for an increased vascular resistance in hypertension is that of structural changes in the resistance essels It has been shown that such st uct ral changes are of g eat hemodynamic importance in established hypertension in man and animal (24 67 81) To study the possible role of this factor as an explanation for the highe resistance in the refractory group compared to the responders blood flow resistanc in the hand and in the calf at maximal dilatation was determi ned As the methods used for dilatation of the hand and calf blood vessels seem to induce an almost compl te r laxation of the smooth muscle cells in the esistance ssels (see page 27) the higher resistance in the hand and in the calf at maximal dilatation in the ef actory group strongly indicated the existance of more severe struct ral vasc lar chang s in the ef acto y g oup tha i the re ponding g oup It is most likely that the struct ral changes i these pati t mai ly a e due to a relative wall thickening i the esistance vessels i e increa ed wall/lumen ratio (24 31 67 72 81) Theo etically the higher esi t nce at maximal dilatation in the ef actory g oup could be due to mor sev re arterio sclerotic change of the big a t ries of those patient The findings of no mal oscillomet ies i the legs and no differenc in blood press e between the left and ight rm i esponders and non responde s cont adict howeve more extensi e a te losclerotic changes in the brachial or femoral a t rie of both groups

The mo e p onounced st uct al asc lar hanges in the ef actory patients compa d to the esponde s could be explained by mo e pronounced changes in the non- esponders befo t eatment Alte nati ely the expl nation could be that the asc l changes though i itially of the same sev ity we e mo e e sible on blood p s e lowe ing the apy (52 68) i the esponding g oup tha i the ef a tory g oup

MINOXIDIL IN THE TRIPLE DRUG TREATMENT OF REFRACTORY HYPERTENSION

M no id i till unde clinical i estig tion and ha been shown to be a oci t d w th a diolo ic ight trium lesions i dogs (15) Howeve

extracellular fluid volume (19 23) In the present patient series there was no significant difference between the refractory and the responding group concerning the total plasma volume nor was there any significant difference between the groups when plasma volume was expressed in ml/cm body height a more reliable and reproducible indicator of intravascular volume (8 73) A trend towards higher values in the refractory group could however be seen and the lack of significance may be due to the small number of patients (Table IX) On the other hand since cardiac output was the same in the two groups and since the increased volume is thought to act on blood pressure via an elevated cardiac output a volume factor explaining the higher pressure in the refractory group seems un likely

All patients in both groups had a high and equal degree of β adrenorecepto blockade as shown by isoproterenol stimulation Furthermore no difference between refractory patients and responders were shown concerning cardiac output heart rate or stroke volume (Table X) Consequently with a sub stantially higher arterial blood pressure the refractory patients had a significantly increased total peripheral resistance in relation to the responders the hemodynamic pattern well known to characterize patients with established hypertension

An increased vascular resistance could either be due to increased smooth muscle tone in the resistance vessels and/or to structural changes in these vessels (24 67) Increased vascular smooth muscle tone can have several explanations i e a higher vasomotor nerve tone increased amounts of circulating pressor substances increased sensitivity to vaso constrictor substances electrolyte differences and/or differences in myogenic tone In the present series the possibility also exists that the antihypertensive drugs affected vascular smooth muscle tone differently in the two groups Concerning the vasodilator used the dose of hydrala zine was the same in the matched pairs As all patients refractory to triple drug treatment were shown to be slow acetylators they should have equal or higher plasma concentrations of the drug than their matched con trols since five of those patients were fast acetylators The peripheral hemodynamic studies indicated that vascular tone in the resting calf muscle was the same in the two groups (vascular tone at rest Table XI) as was the vascular tone in the hand (skin) at rest during functional

CONCLUSIONS

In the p esent study it has been shown that

- acceptable blood press r reduction and good patient adherence can be achieved in a majo ity of hypertensive patients treated at an out-patient hypertension cli ic
- the prevalence of seconda y hype tension in an unselected hypertensive population of middle aged men is low and simple diagnostic tests to identify patients with econdary form of hypertension seem sufficient;
- patients ef actory to t iple dr g t eatme t with di retics propranolol and hyd alazine hav inc eased ascula flow resistance probably ca sed by st uct al changes of the resi tance vessel wall;
- when patient   ef acto y to co entional d ug were gi en a potent asodilating agent mino idil an acceptable blood pressure reduction was achieved The blood p   su   eduction was ca sed by a decreased   sc la   istanc   l ading to   inc eased muscle blood flow; thus
- the mai   so fo the poo hypotensi   r sponse in the refractory patient wa an nc ea d asc la   sistance

it was considered justified to use the drug in the present series of patients refractory to treatment as these patients probably had an impaired prognosis (4 80) The patients were checked frequently but no adverse effects from the treatment were observed except for mild hypertrichosis

Sodium and water retention during minoxidil therapy have previously been described (34 36) No weight gain or plasma volume increase was noted in the present series (Table XIII) implying that in these patients the diuretic treatment was sufficient to counteract the expected plasma volume increase However all patients had normal renal function (Table II) and more potent diuretic therapy might be needed in patients with impaired renal function (49 59)

The β blocking therapy shown to induce an effective blockade of the β receptors by isoproterenol infusions in the patients studied was sufficient to prevent tachycardia anticipated from the minoxidil therapy (Paper IV) That minoxidil caused an increase in cardiac output in spite of β adrenoreceptor blockade can not be ruled out since cardiac output was not determined during minoxidil treatment Blood flow to the calf during rest was increased with about 50 % (Table XIV) This finding might be explained by an increased cardiac output the alternative explanation being an altered distribution of blood flow

All patients previously refractory to treatment had a considerable blood pressure reduction when given minoxidil (Paper IV) This blood pressure reduction was positively correlated to the increase n calf muscle blood flow (Fig 7) and in these patients minoxidil obviously had a vasodilating capacity superior to hydralazine (Table XIV) As no change in blood flow resistance at maximal vasodilatation was demonstrated after the blood pressure reduction with minoxidil the vascular abnormality in these patients did not show a tendency to be reversible as has pre iously been demonstrated in animal studies (52) as well as in man (68) it must be emphasized however that the observation time was probably too sho t for such changes to take place

Patient acceptance of minoxidil in this study was excellent and the drug can be regarded as an alternative in the combination t eatment of ref actory hypertension

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REFERENCES

1 Abernethy J D t The problem of non compli nce in long term nti hype tensive the apy Drugs 11 (Suppl 1) p 86 1976

2 Adler M W d Souza M F and Holland W W The drop-out problem and the effectiveness of popul tion treatment of raised blood pres s re In Pathophysiology and management of te ial hyperten ion Lindgre & Söner AB 1975 p 275

3 Au ll M Be gl nd G Nilsson A nd Suu kOla M Radio enografi vid diagnostik och screenl g' hype te sion In Hyp rtension No diskt symposium i Göteborg 1973 Ed Vedi A Vilhelmsson C and We kö L Lindg en & Söne AB Götebo g 1973

4 Bee er D G Hamilton M Fal man M J and Harpu J E The i fluenc of a tihype te si t eatme t ove the incidence of cerebral ascula disease Postg ad Med J 49 905 1973

5 Berglund G Tibblin G and Aur ll M U ina y no dreneline excre tion and enal function i normal and hype tensive 50 ye r-old men Cli Sci Mol Med 49 485 1975

6 B Bchner Mo tensen J A mple method fo the determination of glo me ula filtration ate Scand J Cli Lab In est 30 271 1972

7 Caldwell J R Cobb S Dowling M D and de Jongh D The drop-out p oblem i antihype t i treatment J Chron Dis 22: 579 1970

8 Chien S Usami S Simmons R L McAllister F F and G egersen M I Blood volume and age epeated mea u ements on normal men aft r 17 ye J Appl Physiol 21 583 1966

9 Conway J A a c i r bnormality i hype tension A study of blood flow the fo re Ci c l tion 27 520 1963

10 Conway J and Palme s M The ascul r effect of the thi zide diure i A h i t Med 111 203 1963

11 De Quatt o V nd Cha Raised plasma catecholamines in some pa en th p mary hype t sion Lanc t I 806 1972

12 De Quat ro V and Mi a Y Ne rogenic factors in human hype ten ion: mechan sm myth? Am J Med 55 362 1973

13 Djoj sug to A M Folkow B Obe g B and White S W A compa ison f blood l ity me su ed i itro and i a scula bed Acta Phy ol Scand 78 70 1970

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Frohlich E D Tarazi R C nd Ulry h M Tilt test for investigating a ne ral component in hype tension Its correlation with clinical charac t ristics Ci culation 36 387 1967

Frohlich E D The adr ne gic nervous system and hyperte sion Mayo Clinic Proceedings 6 361 1977

F yama M : Histometrical investigations of arteries l r f rence to t rial hypertension Tohoku J Exp Med 76 388 1962

Gesenl s H : Oscillog aphie und Arteriogr phie Deutsche Medizin Wochensch 1 1 1949

Giffo d R W E aluation of the hype tensi e patient with emphasis on detecting curable ca s s Milbank Mem Fund Q 47: 170 1969

Gilmo e E Woll J Chidsey C T eatme t of ssential hypertension with a new asodilat i combination with B ad energic blockade N Engl J Med 282 521 1970

5 Glasgow Blood P s e Clinic Jou nal of the Roy l College of Physi ia s of London 7 87 1972

6 Gottlieb T B Katz F H Chids y C A III Combined ther py with v sodilato d ug nd B ad en gic blockade i hype tension A compar tive tudy of minoxidil nd hyd al ine Ci c latio 45 571 1972

7 Hansson L Ol nde R Abe g H Malmc ona R and We terlund A T atment of hype t n ion with prop anolol and hyd al zin Act Med Sc nd 190 531 1971

8 Hansson L d d ene gi blockade in se ti l hype tension Acta Med Scand Suppl 550 1973

19 Han son E Si tsson R P sonal communication

40 Hodge J V Mc Qu E G nd Smi k H Re ult of hypoten i e the py t rial hype ten ion B it Med J 2 1 1961

41 Hood B BjB k S Sanne tedt R and Ange all G Analy is of mo t l ty nd i acti ely t eated hype tensi e dise e Acta Med Scand 174 393 1963

42 Hype on Study G oup Guidelines fo the detection diagnosis and manag me of hype ten ive popul tion Ci c lation 44 263 1971

43 Juli S and scho k M A Bore line hypertension A c itical e iew J C on D 23 723 1971

44 J l S nd E l M Autonomic ne vous c di ascula eg l tion bo d l ypo ten ion An J Ca diol 36 685 1975

45 annel W B Wolf P A V t J and McNamara P M Epidemiologic sc ne f the ol of blood press i st oke the F amingham udy J A M A 214 301 1970

14 Doyle A E Frazer J R E and Marshall R J Reactivity in forearm vessels to vasoconstrictor substances in hypertensive and normotensive subjects Clin Science 18 441 1959

15 DuCharme D W Freyburger W A Graham B E Carlsson R G Pharma cologic properties of minoxidil a new hypotensive agent J Pharm Exp Ther 184 662 1973

16 Duff R S Adrenaline sensitivity in peripheral blood vessels in human hypertension Brit Heart J 19 45 1957

17 Dunne J R Variation of blood pressure in untreated hypertensive out patients Lancet 1 391 1969

18 Dustan H P In The heart and circulation Second National Conference on Cardiovascular Diseases Research 1 p 334 Wash DC Fed Am Soc Exp Biol 1965

19 Dustan H P Tarazi R C and Bravo E L Dependence of arterial pres sure on intravascular volume in treated hypertensive patients N Engl J Med 286 861 1972

20 von Euler U S and Floding I Diagnosis of pheochromocytoma by fluoremetric estimation of adrenaline and noradrenaline in urine Scand J Clin Lab Invest 8 288 1956

21 Evans D A P and White A Human acetylation polymorphism J Lab & Clin Med 63 394 1963

22 Ferguson R K Cost and yield of the hypertensive evaluation Ann Intern Med 82 761 1975

23 Finnerty F A Relationship of extracellular fluid volume to the de velopment of drug resistance in the hypertensive patient Am Heart J 81 563 1971

24 Folkow B Grimby G Thulesius O Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance Acta Physiol Scand 44 255 1958

25 Folkow B Hallbäck M Lundgren Y and Weiss L Structurally based increase of flow resistance in spontaneously hypertensive rats Acta Physiol Scand 79 373 1970

26 Fries E D The hemodynamic effects of hypotensive drugs in man IV 1 hydrazinophtalazine Circulation 8 199 1963

27 Fries E D Hemodynamics of hype tension Physiol Rev 40 27 1960

28 Frohlich E D Ulrych M Taraz R C Dustan H P and Page I H A hemodynamic comparison of essential and reno ascular hypertens on Cardiac output and total peripheral resistance in supine a d tilted patients Circulation 35 289 1967

29 Frohlich E D Ta azl R C nd Ulrych M Tilt test for investigating a eu al component in hyperte sion its co rel clon with clinical charac teristics Circulation 36 387 1967

30 Frohlich E D The adrenergic ervous system and hypertension Mayo Clini P oceedings 6 361 1977

31 Furuyama M Histometrical I vestigations of arteries in ref rence to arterial hypertension Toho u J E p Med 76 388 1962

32 Gesenius H Oscillographie und Arteriographie Deutsche Medizin Wochenschr 1 1 1949

33 Gifford R W Evaluation of the hypertensive patient with emphasis on detecting c able ca se Milbank Mem Fund Q 47 170 1969

34 Gilmor E Well J Chidsey C Treatment of essential hype tension with a new sodil to in combinatio with B ad energic blockade N Engl J Med 282 521 1970

35 Glasgow Blood Press e Cli ic Jou nal of the Royal Coll ge of Phy i cia s of London 7 87 1972

36 Gottli b T B Katz F H Chidsey C A ((Combined ther py with asodilato d ug and B ad ene gic blockade in hypertension A compa a t e t dy of minox dil nd hyd alazine Ci c l tio 45 571 1972

37 Hansson L Olande R Aberg H Malmc ona R and Weste lund A T tme t of hype t ion with p op nolol and hyd alazi Acta Med Scand 190 531 1971

38 Ha son L f Ad ene gic blockad i es ential hype tension Acta Med Scand Suppl 550 1973

39 Har son E S ve t so R P rsonal communication

40 Hodge J V Mc Quee E G and Smirk H Result of hypotensive the apy te l l hype tension B it Med J 2 1 1961

41 Hood B Bjö k S Sanne t dt R and Anger all G Analysi f mo f ty and s l l acti ely t ated hype t si e di ea e Acta Med and 174 393 1963

42 Hype ten on S udy G oup Guideline for the detection diagnosis and manageme f hype t ive pop l tion Circ lation 44 263 1971

43 Juli S nd Scho k H A Bo de line hypert n ion A critical re iew J Ch on D 23 723 1971

44 J l S d E l M Autonomi e vous ca dio ascula egulation bo de l ne hype t ion Am J Ca diol 36 685 1975

45 Ka l d B Wolf P A V t J and McNa a P M Epidemiologic he t of the ol of blood p sure i st ok the F amingham udy J A M A 214 301 1970

14 Doyle A E Frazer J R E and Marshall R J Reactivity in forearm vessels to vasoconstrictor substances in hypertensive and normotensive subjects Clin Science 18 441 1959

15 DuCharme D W Freyburger W A Graham B E Carlsson R G Pharmacologic properties of minoxidil a new hypotensive agent J Pharm Exp Ther 184 662 1973

16 Duff R S Adrenaline sensitivity in peripheral blood vessels in human hypertension Brit Heart J 19 45 1957

17 Dunne J R Variation of blood pressure in untreated hypertensive out patients Lancet 1 391 1969

18 Dustan H P In The heart and circulation - Second National Conference on Cardiovascular Diseases Research I p 334 Wash DC Fed Am Soc Exp Biol 1965

19 Dustan H P Tarazi R C and Bravo E L Dependence of arterial pres ure on intravascular volume in treated hypertensive patients N Engl J Med 286 861 1972

20 von Euler U S and Floding I Diagnosis of pheochromocytoma by fluoremetric estimation of adrenaline and noradrenaline in urine Scand J Clin Lab Invest 8 288 1956

21 Evans D A P and White A Human acetylation polymorphism J Lab & Clin Med 63 394 1963

22 Ferguson R K Cost and yield of the hypertensive evaluation Ann Intern Med 82 761 1975

23 Finnerty F A Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient Am Heart J 81 563 1971

24 Folkow B Grimby G Thulesius O Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance Acta Physiol Scand 44 255 1958

25 Folkow B Hallbäck M Lundgren Y and Weiss L Structurally based increase of flow resistance in spontaneously hypertensive rats Acta Physiol Scand 79 373 1970

26 Fries E D The hemodynamic effects of hypotensive drugs in man IV 1 hydrazinophtalazine Circulation 8 199 1963

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61 Pluss R G Orcutt J Chidsey A Tissue distribution and hypoten si e ffects of minoxidil in normotensi e ats J Lab Clin Invest 79:639 1972

62 Prinzmetal M and Wilson C : The nature of the peripheral resistance in arterial hyperte slo with special reference to the asomotor system J Clin Invest 15: 63 1936

63 Rosenheim M L The treatme t of severe hypertension Br Med J 2: 1181 1954

64 Sanne stedt R : Hemodynamic response to exercise in patients with arterial hype tension Acta Med Scand Suppl 458 1966

65 Sannerstedt R and Conway J Hemodynamic and scular responses to antihypertensive treatment with adrenergic blocking agents A review Am Heart J 79 122 1970

66 Schroede H A : Management of rterial hypertension Am J Med 17 540 1954

67 Si e tsson R The hemodynamic import nce of struct al ascular hang s l s enti l hypertension Acta Physiol Scand Suppl 343 1970

68 Si tsson R and Ha sson L Eff ts of blood p ss re reduction on the st t l s la abnormality in skin and muscle ascular beds in human sse tial hype tension Clin Sci Mol Med 51: 77 1976

69 Smi k H Result of methonium t eatment of hype tensi e patients B it Med J 1 717 1954

70 Smi k H Hamilton M Doyl A E and McQueen E G The treatment of hype t l e hea t f llu e nd of hypertensive cardiac overload by blood p es r ducti Am J C diol 1 143 1958

71 Staml R Staml J C lnelli J Pritchard D Gosch F C Ti ho S Re ti o B nd Fine D Adhe ence and blood p essu e response to hype t sion t eatme t Lanc t Dec 20 1227 1975

72 Suwa N nd Takaha hi T Mo phological and mo phometrical analysis of i c i tion i hype tension and ischaemic kidney Urban & Schwar en be g München Be li -Wi 1971

73 T zi R C Du tan H P Frolich E D et al Plasma volume and ch on hype t ion Rel tionship to a te ial p ss le els i d ff ent hyp ten i di ase Arch I t Med 125 835 1970

74 T R C Dust H P and F ohlich E D Long term thiazide the py s ent l hype te sion E idence fo persiste t alte ation pl sma volume and nin acti ity Ci c lation 41: 709 1970

75 T bbl G Be gentz S E Bj e J and Wilhelmse L Hematoc it plasma p t in pl sma volume and viscosity in early hypert si e di ease Am Hea t J 72 165 1966

46 McKee P A Castelli W B McNamara P M and Kannel W B The natural history of congestive heart failure the Framingham study N Engl J Med 284 1441 1971

47 Lawson H C Handbook of Physiology section 2 vol 1 p 23 American Physiological Society Washington 1962

48 Lee R E Seligmann A W Clark M A and Rousseau P A Freedom from cerebral vascular accidents during drug induced blood pressure reduction in benign hypertensive disease Am J Cardiol 11 738 1963

49 Limas C J and Freis E D Minoxidil in severe hypertension with renal failure Effect on its addition to conventional antihypertensive drugs Am J Cardiol 31 355 1973

50 Louis W J Doyle A E and Anavekar S Plasma norepinephrine levels in essential hypertension N Engl Med 288 599 1973

51 Lund Johansen P Hemodynamic pattern in essential hypertension at rest and during muscular exercise Acta Med Scand Suppl 472 1967

52 Lundgren Y Regression of structural cardiovascular changes after reversal of experimental renal hypertension in rats Acta Physiol Scand 91 275 1974

53 Maher J R Whitney J M Chambers J S and Stanonis D J The quantitative determination of isoniazid and para amino salicylic acid in body fluids Am Rev Tuberc 76 852 1957

54 McNeil B J Varady P D Burrows B A and Adelstein S J Measures of clinical efficacy Cost effectiveness calculations in the diagnosis and treatment of hypertensive renovascular disease N Engl J Med 293 216 1975

55 McNeil B J and Adelstein S J Measures of clinical efficacy The value of case finding in hypertensive renovascular disease N Engl J Med 293 221 1975

56 Menlolwitz M and Natchie N Work of digital vasoconstriction produced by infused nor epinephrine in primary hypertension J Appl Physiol 13 247 1958

57 Morrison B Parenteral hexamethonium in hypertension Br Med J 1 1291 1953

58 Perry H M Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis Am J Med 54 58 1973

59 Pettinger W A Mitchell H C Minoxidil an alternative to nephrectomy for refractory hypertension N Engl Med 289 167 1973

60 a) Pickering G High blood pressure J & A Churchill Ltd Sec ed 1968 p 52

b) " p 89

76 Tibblin G High blood pressure in men aged 50 a population study of men born in 1913 Acta Med Scand Suppl 470 1967

77 Truett J Cornfield J and Kannel W B A multivariate analysis of the risk of coronary heart disease in Framingham J Chron Dis 20 511 1967

78 Tobian L Why do thiazide diuretics lower blood pressure in essential hypertension? Ann Rev Pharmacol 7 399 1967

79 Veterans Administration Cooperative Study Group on Antihypertensive Agents Effect of treatment on morbidity in hypertension J A M A 202 116 1967

80 Veterans Administration Cooperative Study Group on Antihypertensive Agents Effects of treatment on morbidity in hypertension III Influence of age diastolic blood pressure and prior cardiovascular disease further analysis of side effects Circulation 45 991 1972

81 Weiss L Aspects of the relation between functional and structural cardiovascular factors in primary hypertension Experimental studies in spontaneously hypertensive rats Acta Phys Scand Suppl 409 1974

82 Whitney R J The measurement of volume changes in human limbs J Physiol 121 1 1953

83 WHO Expert committee on arterial hypertension and ischaem c heart disease Tech Rep Ser No 231 Geneva

84 Wilber J A and Barrow J G Reducing elevated blood pressure Experience found in a community Minn Med 52 1303 1969

85 Wilhelmsen L Tibblin G and Werkö L A primary preventive study in Gothenburg Sweden Preventive Medicine 1 153 1972

86 Wilhelmsen L Berglund G and Werkö L Prevalence and management of hypertension in a general population of Swedish men Preventive Medicine 2 57 1973

87 Wilhelmsen L Wedel H and Tibblin G Multivariate analysis of risk factors for coronary heart disease Circulat on 48 950 1973

88 Wilhelmsen L Ljungberg S Wedel H and Werkö L A compar son of participants and non participants in a primary prevent ve trial J Chron Dis 29 331 1976

89 Zacest R Gilmore E and Koch Weser J Treatme t of essent al hypertension with combined vasodilatation and β adrenergic blockade N Engl J Med 286 617 1972

90 Åblad B A study of the mechanism of the hemodynam c eff cts of hydralazine in man Acta Pharmacol Toxicol 20 Suppl 1 1963

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By Ólafur Jensson

FROM THE BLOOD BANK, STATE HOSPITAL,
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Studies on Four Hereditary Blood Disorders in Iceland

By
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PRINTED IN ICELAND
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Acta Medica Scandinavica

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Læknadeild Háskóla Íslands hefur á fundi sínum 9. nóvember 1977 samþykkt að taka ritgerð þessa gilda til doktorsprófs

Ólafur Bjarnason
deildarforseti

INTRODUCTION

I had the good luck of being enrolled as a postgraduate student for one year in a course in Clinical Pathology at the Royal Postgraduate Medical School at the Hammersmith Hospital in London 19[illegible]–1950. I am always thankful to Dr med Olafur Bjarnason, professor of Pathology at The University of Iceland for arranging this. My second stroke of luck occurred when my desire to continue my postgraduate studies in haematology was fulfilled and late Professor J. H. Dible found a place for me as a voluntary research worker in the Department of Haematology at the R.P.G.M.S. 1956–1957 under Professor Sir John's leadership. These two years at the Hammersmith Hospital were decisive for my later work at home in Iceland. On several occasions during the years of study when I have made pilgrimage to the R.P.G.M. School professor Sir John has made arrangements for me to review my work at different stages at departmental meetings and his chief in haematological technology Mr L. H. Wallott even visited Iceland in 1969 to assist me with the investigations on von Willebrand's disease supported by the NOVO fund in Denmark.

Investigation of three conditions reviewed in this paper hereditary elliptocytosis, hereditary spherocytosis and von Willebrand's disease began in 1958 when the author was a consultant in haematology to the City Hospital in Reykjavík for several months. Chief of the medical department Dr med Oskar Th. Thordarson offered me valuable opportunities in the beginning which were to guide me onto a path in human genetics. My work in haematology since 1959 for the Hospital in Akureyri, chief of the medical department Dr. Olafur Sigurdsson, has been most valuable. In addition to my participation in diagnostic haematology in hospitals in and outside Reykjavík from 1959–1975 I can only express my thank to the numerous colleagues, medical technologist and hospital secretaries who have shown understanding and given me much assistance in my research.

My main laboratory facilities have been my private laboratory for haematology and clinical cytology housed in Domus Medica Reykjavík since 1965, which has offered diagnostic service to general practitioners, specialists and hospitals from 1959.

As a director of the Blood Bank from 1st of March 1972 my position to carry on with research in human genetics has improved and given me and my collaborators more opportunities and facilities to extend previous studies and add new items to our research in this field.

I acknowledge the understanding and support of the Ministry of Health and Governing Committee of the State Hospitals (University Clinic) to me and my coworkers investigations.

This review has been accepted by the Medical faculty of the University of Iceland for a M.D. degree.

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Hereditary elliptocytosis
Hereditary spherocytosis
Pelger anomaly
Von Willebrand s disease

Nine publications on these disorders are listed below and designated by Roman numerals *which will be used for reference in the text*

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V Jensson Ó., Árnason K. Íslensk Pelger fjölskylda. Læknablaðið 60 98-103, 1963

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HEREDITARY ELLIPTOCYTOSIS IN ICELAND

In 1964 the first 35 cases of hereditary elliptocytosis in Iceland were reported in the Icelandic Medical Journal (I) In this paper the main features of this hereditary disorders were reviewed with reference to several of the classical papers on this condition Pedigree data presented in this paper was later developed in more detail (III) Some 170 kindred were scanned for the elliptocytic trait in the first phase of work on the kindred under study most of whom could be found in a book (Genealogical record) published in 1951 (Árnadóttir)

The second paper on this kindred was published in the British Journal of Haematology in 1967 (III) Over 400 individuals belonging to a large family had been examined for the elliptocytosis trait, mostly by inspecting a stained blood film It was not able that seven of the 50 elliptocytic individuals diagnosed up to that time were detected in hospitals and 43 found by survey of relatives

The pedigree of the Icelandic elliptocytic family (III) is shown in Fig 1 and its geographic orgin on The Map of Iceland page 10

Linkage studies on the elliptocytic family (III)

As stated in the paper (III) 1967 data on linkage was collected from over 100 individuals belonging to 38 sibships in the elliptocytotic family Professor J H Edwards suggested referring samples to Professor Harry Harris and Dr E. B Robson at the Galton Laboratory and Dr T E Cleghorn at the North London Blood Transfusion Centre Edgware Middlesex who determined many marker systems on blood samples from the family members sent by air from Iceland to London The marker systems investigated are shown on 2 punchcards (Fig 2) which were used for the linkage data collected

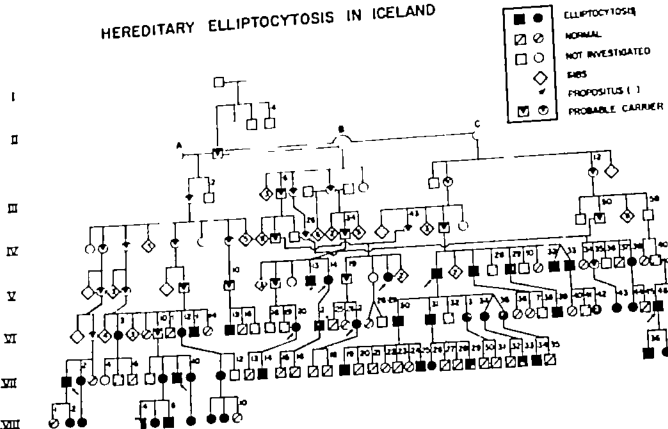


Fig 1 Pedigree of the family

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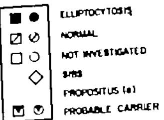
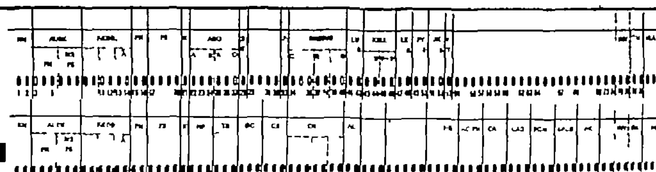


Fig 1 Pedigree of the family

The analysis of the linkage data was done on 23rd of December 1974 by Professor J H Edwards who used his linkage programme and the computer in Leiden by courtesy of Professor Dr J J van Rood, Dept. of Immunohaematology University Hospital Leiden Holland


Fig 2 Card I 1 21 identification 22 53 blood group data.
Card II 1 21 identification 22 78 biochemical genetic markers

The 11 loci analysed in 29 suitable elliptocytic family units were ABO MNS P Rh Lewis bloodgroup systems acid phosphate peptidases phosphoglucomutase 1 adenylate kinase and haptoglobins

The results (see Lod scores table 1) show no linkage between elliptocytosis locus in this family and other marker systems analysed

It has been known since 1953 (Goodall Hendry Lawler and Stephen 1953 Marshall Bird Bairley and Beckner 1954 *and Morton* 1956) that at least two varieties of hereditary elliptocytosis exist, one which is linked to the Rh blood group system locus on chromosome No 1 and another which is not linked to the Rh blood group locus The Icelandic elliptocytosis family is thus a good example of the latter non-linked variety

Recombination fraction	0 1	0.3	No. of scoring families
ABO	-0.868	-0 145	4
MNS	-0 413	-0.006	6
P	-0 462	-0 0	11
Rh	1.399	-0 169	5
Haptoglobin	0.068	0.032	2
Phospho-glucomutase 1	-0 041	-0.010	1
Acid phosphatase	1 714	-0.276	7
Adenylate kinase	0.013	0 093	2

Table 1

Results of linkage analysis of various loci and elliptocytosis

Results in Lods Close linkage with AcPh and Rhesus excluded

ALGERIAN ICELANDIC FAMILY WITH HEREDITARY ELLIPTOCYTOSIS

An Algerian-Icelandic family with hereditary elliptocytosis, reported in The Icelandic Medical Journal 1964 (II) is reviewed in some detail because it has not been published in English.

The propositus, a boy was at the age of 3 months when diagnosis of elliptocytosis was made His 2½ year old sister and his mother had morphologically normal red corpuscle. The father an Algerian, had elliptocytosis, but no haematological changes indicating haemolysis. Test for sickling (wet wax sealed preparation) was negative in all four members of the family

The results of haematological investigation made on this family are recorded in

Table 1

Haematological findings in the Algerian-Icelandic family Three observations on the son in in the 1st year

Family	Age	Condition	Hb g/100 ml	Haemato-crit %	RBC	MCV	MCHC	Reticulo-cytes %
	27	Elliptocytosis	14.9	45	5.40	83	33	0.8
	24	Normal	10.8	34	3 72	81	31	0 7
Daughter	2½	Normal	11 1	36	—	—	31	0.9
Son	3/12	Elliptocytosis	9.3	33	3 15	104	28	5.5
Son	4/12		9.0	31	3 76	80	29	8.0
Son	10/12		10.2	33	4.50	75	31	6.4

Table 2

Blood groups and biochemical genetic markers of the Algerian-Icelandic family

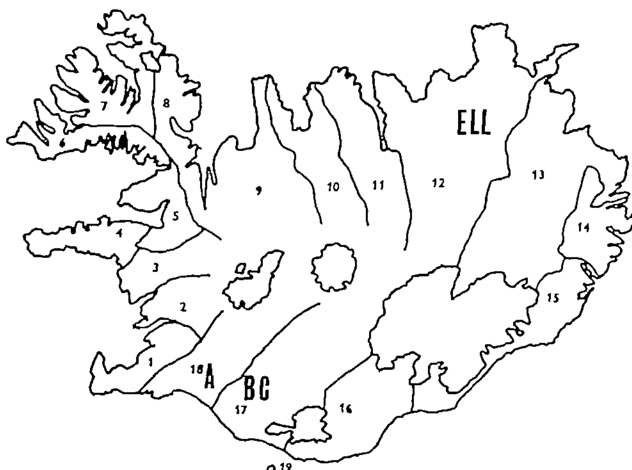
Blood groups	Father	Mother	Daughter	Son
ABO	0	0	0	0
Rh	cDe/cde	cde/cde	cde/cde	cde/cde
MN Ss	MNss	MNss	MNss	NNss
P	++	++	++	++
Lutheran	—a	—a	—a	—a
Kell	neg	neg	neg	neg.
Lewis	a—b+	a+b—	a—b+	a—b+
Duffy	—a	—a	—a	—a
Kidd	+a	+a	+a	+a
Biochemical Markers				
Haptoglobin	2-2	1 1	2 1	2 1
Transferin	C	C	C	C
Serum cholinesterase (U Usual)	U	U	U	U
Acid phosphatase	BA	B	BA	BA
Phosphoglucorate dehydrogenase	A	A+B	A+B	A+B
Phosophoglucomutase	1	1	1	1

table 1 and blood groups and biochemical genetic marker systems done at M R C Human Biochemical Genetics Research Unit and Dept Biochemistry King s College London (Professor H Harris) and at North London Blood Transfusion Centre Edgware Middlesex (Dr T E Cleghorn) are shown in table 2

No linkage was suggested between the elliptocytosis main locus and the Rh blood group system in this family and other makers tested for were uninformative

The affected boy had mild well compensated haemolytic anaemia during his first year On several occasions from 1964-1974 his haematological values have been within normal range for his age

The author has no knowledge of the occurrence of hereditary elliptocytosis in Algeria



Map of Iceland
Geographic orgin of the Icelandic elliptocytic family is found in county 12 ELL.

The homesteads of the von Willebrand's disease families A, B and C are found in counties 18 and 17

HEREDITARY SPHEROCYTOSIS

Studies on hereditary spherocytosis HS in Iceland (IV) contain clinical haematological and genetic data on 30 HS cases in 12 families. In addition 70 members of HS families have been surveyed haematologically. Symptoms and signs of HS have been searched for in all available family members. Genealogical information has been obtained from family members, genealogists and by study of many published Icelandic genealogical records.

The population of Iceland, which is Caucasian and mainly originated from Norway, Ireland and Scotland (Bjarnason et al. 1971) was just over 216,000 in December 1974.

HS is the most common hereditary haemolytic disorder in Caucasian peoples. Estimated prevalence of all humans is one in five thousand (1/5000) (Jacob 1972). Accordingly one would anticipate to find approximately 40 individuals with HS in the present population of Iceland. From 1945-1974 30 individuals with HS have been diagnosed, three of whom have died in 30 years covered by the present study.

As we have on record over 70 individuals with hereditary elliptocytosis which can with high probability be traced to single mutation in the past (see above) this haemolytic condition is the more common one of the two at this stage of knowledge.

Pedigree Studies

Seven HS families 1-3, 11 and 9 show the relationship of 23 HS family members (Fig 1-7). Families of seven HS cases have not been drawn up.

In families 2, 3 and 11 available genealogical information made it possible to draw up rather large pedigrees. These families form the basis for continued research on HS in Iceland along with the smaller HS families found.

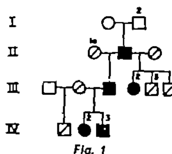


Fig. 1

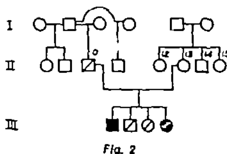


Fig. 2

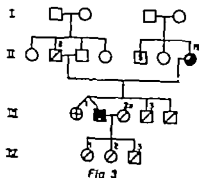


Fig 3

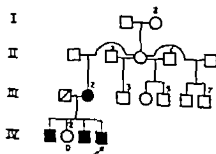


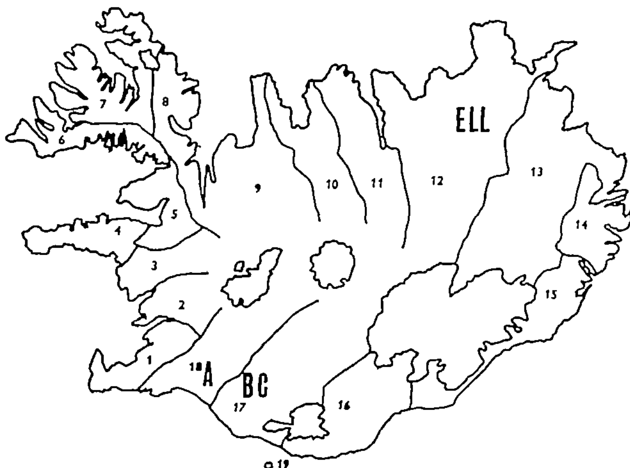
Fig 4

table 1 and blood groups and biochemical genetic marker systems done at M.R C Human Biochemical Genetics Research Unit and Dept Biochemistry King s College London (Professor H Harris) and at North London Blood Transfusion Centre Edgware Middlesex (Dr T E Cleghorn) are shown in table 2

No linkage was suggested between the elliptocytosis main locus and the Rh blood group system in this family and other makers tested for were uninformative

The affected boy had mild, well compensated haemolytic anaemia during his first year On several occasions from 1964-1974 his haematological values have been within normal range for his age

The author has no knowledge of the occurrence of hereditary elliptocytosis in Algeria



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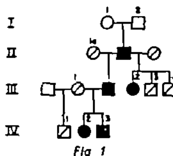


Fig 1

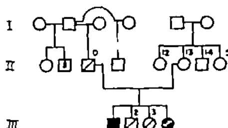


Fig. 2

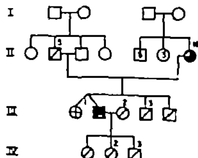


Fig 3

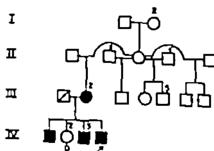


Fig. 4

Table 1 Main Symptoms Signs and Laboratory Observations in 22 Patients with HS before Splenectomy

Case Nr./Family Nr	1/1	2/1	3/1	4/1	5/1	6/2	7/2	8/2	9/2	10/3	11/3	12/3
Sex	M	M	F	F	M	F	F	M	M	M	F	F
Age	41	16	7	2	4	46	22	5	4	58	16	19
Anæmia	+		+	+	+	+	+	+	+	+	+	
Jaundice	+		+	+	+	+	+	+	+	+	+	
Gallstones										+		
Splenomegaly	+		+			+			+	+	+	
Spherocytes	+	+	+	+	+	+	+	+	+	+	+	+
Reticulocytes %	10 7			17 0	13.0	14.2		10.0		40.0	1.0	3.5
Hæmoglobin g/100 ml	12 4		7.5	4.3	6.3	8.0		9.3	11.0	9.6	3.0	11.5
Bilirubin mg/100 ml				2.5		1.5		3.65	1.5	2.25		1.2
Coomb s test				—	—	—						
Osmotic fragility	+		+	+	+	+			+			+
Aplastic crisis						+					+	
Weight of Spleen	925	E.L.	255	80	170	580	300	300	160	775	1 700	250
Accessory Spleen												

Enlarged

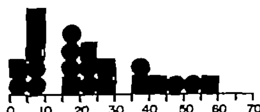


Fig 8 Age (y) of HS patients at the time of splenectomy Squares = males circles = females

	HS cases unoperated	Influenza Aplastic crisis
Females	5	3
Males	4	1 (died)
Total	9	4

Table 2 HS cases at risk during the influenza 1957 1958

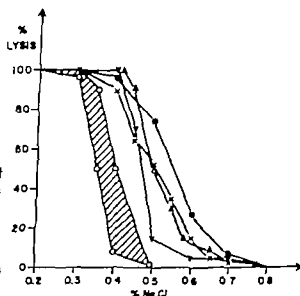


Fig 9 Red cell fragility of 4 typical HS patients in family 1 (Fig 1) and family 5 (Fig. 3) Striped area shows the normal range

14/4	16/5	17/6	18/7	19/8	25/10	26/11	27/11	28/11	29/12
F	M	F	M	F	M	F	M	M	F
22	35	7	8	35	27	51	27	21	15
+	+	+	+	+	+	+	+	+	+
+		+	+		+	+	+	+	+
+						+		+	
	+				+	+		+	
+	+	+	+	+	+	+	+	+	+
7.7	5.5	10.3	11.0	7.0		12.4	13.3	22.0	
10.5	4.0	10.7	8.0	9.0	12.4	11.8	13.3	12.4	
2.3	1.7	4.8	2.1	1.2	3.4	1.9	3.8	6.4	
—	—	—	—	—	—		—	—	—
+	+		+	+					
+	+								
180	1 150	340	200	280	1.285	600	470	1 400	375
		+	+				+	+	+



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Case Nr./Family Nr	1/1	2/1	3/1	4/1	5/1	6/2	7/2	8/2	9/2	10/3	11/3	12/3
Sex	M	M	F	F	M	F	F	M	M	M	F	F
Age	41	18	7	2	4	46	22	5	4	58	18	19
Anæmia	+		+	+	+	+	+	+	+	+	+	
Jaundice	+		+	+	+	+	+	+	+	+	+	
Gallstones										+		
Splenomegaly	+		+			+			+	+	+	
Spherocytes	+	+	+	+	+	+	+	+	+	+	+	+
Reticulocytes %	10 7			17 0	13.0	14.2		10.0		40 0	1.0	3.5
Hæmoglobin g/100 ml	12 4		7.5	4.3	6.3	8 0		9.3	11 0	9.6	3.0	11.5
Bilirubin mg/100 ml				2.5		1.5		3.65	1.5	2.25		1.2
Coomb s test				—	—	—						
Osmotic fragility	+		+	+	+	+			+			+
Aplastic crisis						+					+	
Weight of Spleen	925	E.L.	255	80	170	580	300	300	160	775	1 700	250
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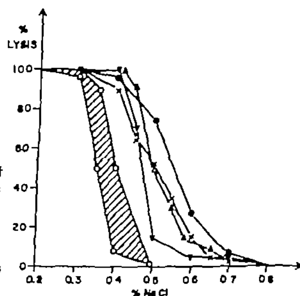


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F	M	F	M	F	M	F	M	M	F
22	33	7	6	35	27	51	27	21	15
+	+	+	+	+	+	+	+	+	+
+		+	+		+	+	+	+	+
+						+		+	
	+				+	+		+	
+	+	+	+	+	+	+	+	+	+
7 7	5.5	10.3	11.0	7.0		12.4	13.3	22.0	
10.5	4.0	10.7	6.0	9.0	12.4	11.8	13.3	12.4	
2.3	1 7	4.8	2 1	1.2	3 4	1.9	3.8	6.4	
—	—	—	—	—	—		—	—	—
+	+		+	+					
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180	1 150	340	200	290	1.285	600	470	1 400	375
		+	+				+	+	+

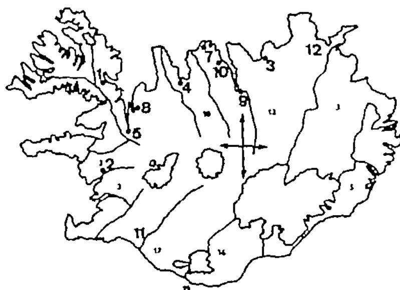


Fig. 10 Map of Iceland. Geographic origin of 10 HS families indicated by asterisks and Arabic numerals.

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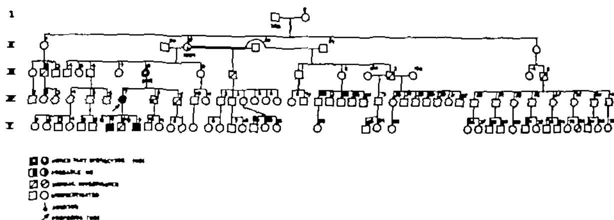


Fig 5 Family 2

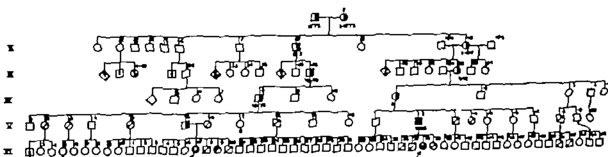


Fig 6 Family 3 Symbols as in Fig 5

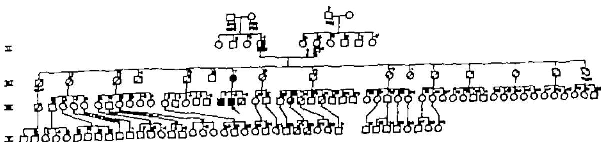


Fig 7 Family 11 Symbols as in Fig 5

STUDIES ON THE PELGER ANOMALY IN ICELAND

The first Icelandic family containing twelve members with *Pelger anomaly* were reported in 1963 (V)

As many members of the Pelger family had been living in a comparatively isolated district for *several generations high frequency* of the Pelger gene in the district was suspected. This led to a survey of 1197 of total of 1441 individuals (83 per cent) living there in 1964 No additional Pelger anomaly individuals were detected in the medical district.

In April 1975 a female born 1944 was diagnosed in a mental hospital in Reykjavík with *Pelger anomaly She and her father* who had the anomaly had ancestors in common with the members of the Pelger family previously reported (VII)

Pedigree Studies

With the aid of two large Icelandic family records published (Jónsson 1953 Magnússon 1960) and a record of lawyers in Iceland (Jónsson 1963) it has been possible to *trace the two branches of this family to* common ancestors born 200 years ago (Fig 1 pedigree drawing).

The homestead of the two family branches is shown in Fig 2, the one detected in 1975 lives in the Eastfjords.

American-Icelandic family with Pelger anomaly

The Pelger anomaly was found in another *family in 1974 (VI) The mother* an American married to an Icelander and her youngest child of four a boy had the anomaly The findings are shown in table 1 and 2.

Table 1 Results on the American-Icelandic Pelger family members.

Family member Year of birth	Father 1939	Mother 1944	Daughter 1962	Daughter 1964	Son 1965	Son 1970
Haematologic Observations						
Condition	Normal	Pelger	Normal	Normal	Normal	Pelger
E.S.R.	3	2	8	5	7	3
Haemoglobin g/100 ml	15.0	12.0	13 0	13.4	13.0	9.8
Haematocrit %	45	40	37	40	39	31
MCHC	33	32	35	34	33	31
WBC	11600	7200	8500	6600	9400	5200
Differential Count						
Stab form %	3	37	2	4		9
Bilober	23	32	28	28	22	27
Trilober %	38	1	35	28	24	0
Quatrilober %	4		8	2		
Lymphocytes %	28	28	27	34	41	54
Monocytes %	8	4	2	2	6	6
Eosinophils %	0	0	0	6	7	4
Basophils	0	0	0	0	0	0

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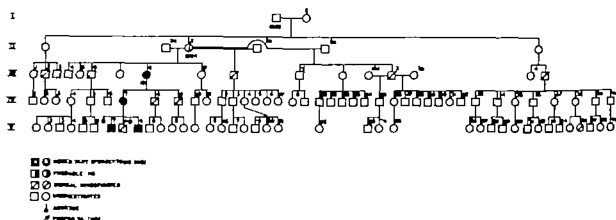


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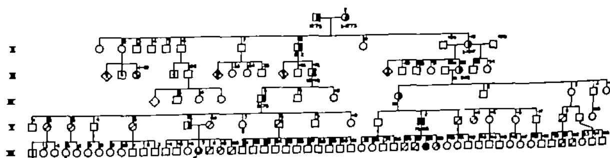


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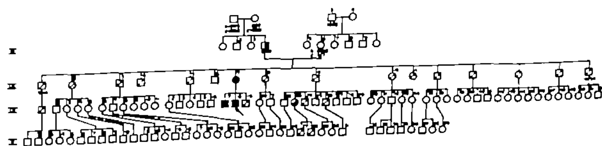


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Quatrilober %	4		6	2		
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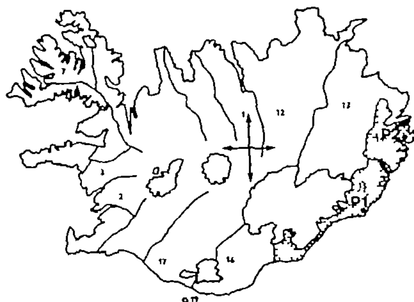


Fig 2. — Map of Iceland. Homesteads of the two branches of the Pelger family: *P 1* detected in 1962 and *P 2* in 1975.

Table 2 Results on the American-Icelandic Pelger family members.

Family member	Father	Mother	Daughter	Daughter	Son	Son
Year of birth	1939	1944	1962	1964	1965	1970
Condition	Normal	Pelger	Normal	Normal	Normal	Pelger
Biochemical genetic markers						
Serum esterases	usual	usual	usual	usual	usual	usual
Haemoglobin	A	A	A	A	A	A
Haptoglobin	1—1	2—1	2—1	1—1	1—1	2—1
Transferrin	C	C	C	C	C	C
Blood groups						
ABO	O	A_1B	A_1	B	A_1	B
Rh	R_2r	R_1r	R_1r	rr	R_2r	rr
MNSs	MsNs	MsMs	MsMs	MsNs	MsMs	MsNs
Kell	neg	neg	neg	neg	neg	neg
Fy^a	+	+	+	neg	+	+

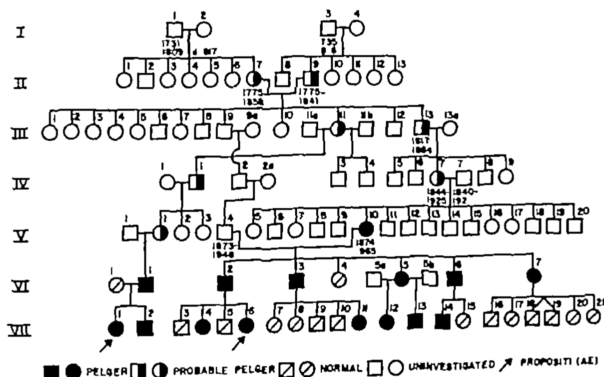


Fig 1 Pedigree of the Icelandic Pelger family



Fig 2. — Map of Iceland. Homesteads of the two branches of the Pelger family: *P 1* detected in 1982 and *P 2* in 1975.

VON WILLEBRAND S DISEASE IN ICELAND

In 1959 a boy was admitted to the Municipal Hospital in Reykjavik with bleed ing tendency His clinical history his family history and a few laboratory tests done at that time pointed to von Willeband s disease Coagulation studies on this family had to be put off until 1969 In that year a second family originated from the same district as the first, was investigated due to similar symptoms and signs (VIII) The third family from the same district was brought to attention when an eleven year old girl was admitted to the University Clinic (Landspitalinn) in July 1969 due to persistent vaginal bleeding for three weeks following her first menstruation (IX)

These families are illustrated in the pedi gree drawings family A, Fig 1 (VIII) family B Fig 2 and family C Fig 3 (IX)

The survey of relatives for clinical symptoms of bleeding tendency covered 120 individuals in Family A. Of these a total of 41 family members belonged to nine sibships which contained one parent affected Results of coagulation tests on 15 members of Family A is recorded in table 1 Coagulation studies on two members in a branch of this family living in America performed by the late Judith G Pool at the Stanford Medi cal Center in California and on two others done in Iceland showed disproportionate rise of factor VIII following infusion of factor VIII concentrate (VIII)

One of the members in Family A, III 12 who transmitted the von Willeband s disease gene to her children also had typical hereditary haemorrhagic telangiectasia lesions in the oral cavity and gastric mucosa (Quick 1974)

Of 80 family members of Family B and C surveyed for clinical symptoms of bleeding tendency 45 belonged to family units in which one of the parents and/or one or more sibling were affected Results of coagulation tests done on 4 members in Family B and 10 members in Family C are shown in table 2 In Fig 4 factor VIII values found in 28 members of the families A, B and C are compared The male members of three families manifest more severe clinical symptoms of bleeding than the females and they also tend to have lower levels of factor VIII A total of 27 individuals have been ascertained as affected 17 males and 10 females

The variability in clinical symptoms and in the levels of factor VIII and in addition the uneven genetic ratio apparent, suggests that the mutant gene is present in latent form in some of the members of the three families studied.

It is thought probable that the mutant gene present in the three von Willebrand's disease families has originated from a common progenitor in the area Efforts to find such a relationship by genealogical approach have not been successful yet. Geographic orgin of the three families is shown on the map of Iceland page 10



Fig 4 — Factor VIII values estimated in 28 individuals in families A B and C

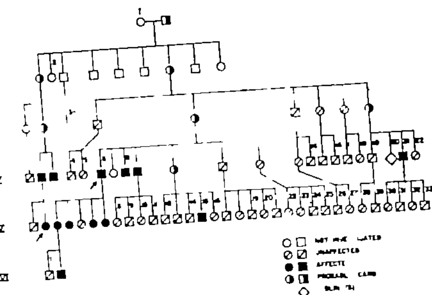


Fig 1 Family A.

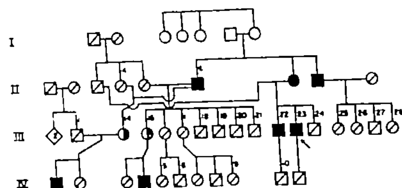


Fig 2 Family B.

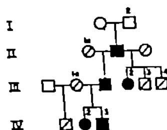


Fig. 3 Family C.

DISCUSSION

It is generally agreed that the four hereditary conditions studied hereditary elliptocytosis von Willebrand s disease the Pelger anomaly and hereditary spherocytosis (HS) show autosomal mode of inheritance (Wintrobe 1975 Britton 1974 Dacie 1960 Hardisty and Ingram 1965)

In each of these conditions Icelandic families have been studied who by genealogical information obtained indicate that the mutant genes causing these disorders and present in the investigated living family members has been transmitted through at least six genearations or 150-200 years The origin of these families has been traced to particular areas in Iceland The relationship of affected family members and their common geographical origin is considered to suggest, that the same type of mutant gene is transmitted in these families Direct biochemical methods explaining the precise nature of the abnormality caused by these mutant genes are presently not available for any of the four hereditary conditions studied Therefore direct proof or disproof of the genetic homogeneity of the conditions under study is not possible

Ascertainment of the affected family members is based on morphological features of the blood cell mainly (in hereditary elliptocytosis Pelger anomaly and HS) and abnormal plasma coagulation factors in the case of von Willebrand s disease

Variants of each of these hereditary condition have been described by many workers indicating possible genetic heterogeneity The demonstration of genetic heterogeneity of hereditary elliptocytosis by linkage studies referred to previously is the only proof of genetic heterogeneity in the four hereditary conditions studied

Hereditary elliptocytosis

In the Icelandic family with elliptocytosis (III) not closely linked to the Rh blood group loci (Cf linkage studies) the morphological features of the red cell have made ascertainment easy The expected one to one genetic ratio is fullfilled and the clinical findings in affected family members at various ages indicate no apparent selection against the elliptocytic members or shortening of their life span

The considerable variation in symptoms and signs of the affected family members is found both within the same sibship or between sibships in different branches of the elliptocytic family (III) The cause of this variation can be explained by non-genetical factors such as infection in some cases while in other cases genetic make-up is probably the main cause for this variation

It has been suggested that hereditary elliptocytosis not linked to the Rhesus blood group system gave rise to more symptoms and signs of haemolysis than the Rh linked variety (Bannermann and Renwick, 1962)

Transient red cell morphological changes were studied in newborn male twins who both developed hyperbilirubinaemia on the first and second day after birth One of the twins underwent exchange transfusion (Jensson et al 1976 unpublished observations) Their father has elliptocytosis (VI 46 see Icelandic family with elliptocytosis) Their red cell blood picture was very pleomorphic for the first 4-6 weeks but by the age of 3-4 months both twins had developed typical elliptocytotic blood picture (Austin and Desforges 1969) Hereditary elliptocytosis as well as HS (Burman 1958) are among many hereditary red cell defects which can give rise to excessive neonatal jaundice in addition to haemolytic disease of the newborn due to immunological causes (Stamey Diamond 1957 Kostinas et al 1967 Oski 1974)

Hereditary spherocytosis (HS)

Apart from typical HS cases in relatively small families showing a dominant mode of inheritance (Meulengracht 1922 Race 1942 McKusick, 1968) three large HS families have been studied in whom typical HS cases have been diagnosed in different branches and thought to contain members with mild HS or HS in an undiagnosable form (Butterworth et al 1950 Carruthers 1960 Dacie 1960) The mild or equivocal forms of HS are

commented on by Dacie, 1960 p 107 as follows. "Subsequent writers have tempted to overlook the possibility of the extremely mild forms described by Gänsslen" (Gänsslen 1922, 1925 1928 cf Dacie s references 1960)

From the present study of families 2, and in particular 3 and 11 the presence of mild HS cases is highly suggestive

When family members in four generations belonging to HS families 2 and 11 (Table VI) are added up, half of the 169 individuals entered as "normal" or approximately 85, could theoretically be affected. Only 7 of the 9 members listed as affected have been diagnosed suffering from HS and two are entered (parents) as probably affected (IV)

The present data are suggestive of a much higher frequency of the HS gene or genes than is indicated by overtly affected HS cases admitted to hospitals The hospital frequency shows probably only the tip of the iceberg and not the true HS gene frequency in the population. From the present study of families 2 and in particular 3 and 11 one is inclined to consider the prevalence of HS gene or genes mainly due to the presence of mild forms of HS which, by a presently unexplained mechanism, can occasionally cause severe typical forms of HS in one or more family units within the "mild" gene family

Admittedly only 38 of the 169 family members recorded in Table VI have been studied haematologically at this stage. But the results so far obtained (Table IV) and discussed above illustrate the difficulties in making ascertainment in extremely mild cases of HS by laboratory methods presently available

Pelger anomaly

Of the ambulatory patients scanned by one of us (O J) referred by practising family physicians and specialists approximately 90 are from Reykjavik and neighbouring municipalities and counties. Individuals from more distant places, over 30 km from Reykjavik form insignificant part of the number surveyed. A few inhabitants from the most remote counties in the north, east and south-east of Iceland are amongst the 40,000 scanned for the Pelger anomaly and recorded in Table 1 in VII.

In this century there has been a great movement of Icelanders from various rural parts of Iceland to the coastal villages and municipalities and in particular to the capital and surrounding areas in the south-west of Iceland

The representation of people from the north-eastern and eastern parts is probably less in the present population living in Reykjavik and the surrounding area, than from most other parts of Iceland. It is therefore probable that further scanning of individuals from the east and north-east part of the country will add new information as to the Pelger gene distribution and frequency in Iceland

On the basis of present results it is considered most probable that the Pelger anomaly gene has been present in Icelanders over 200 years at least The scanning of relatively large sample of the population of Iceland makes it also possible, that the large Pelger family described contains the only mutation of this kind in Icelanders.

Distribution of the Pelger anomaly is worldwide and its frequency ranges from as high as 1 in 1000 persons to one in 10 000 (Johannsson, 1963, Wintrobe, 1974).

Acquired Pelger anomaly has been described by many investigators (Jóhannsson, 1963) mainly associated with development of leukaemia. Such changes in the neutrophil leucocytes have been found in one Icelandic family associated with abnormal blood marrow clone (Kaur et al 1972).

Von Willebrand's disease (v W)

The variation in symptoms and signs and in the results of coagulation and bleeding tests in the v W Icelandic families studied is in accord with most other workers who have studied this condition in the last 20 years (Nilsson et al 1959 Rizza 1975 Nilsson and Holmberg 1975)

The application of the more recent laboratory methods in particular immunoelectrophosis (Stites et al 1971 Zimmerman et al 1971 Rizza, 1975) make it possible to distinguish mild haemophilia A

DISCUSSION

It is generally agreed that the four hereditary conditions studied hereditary elliptocytosis von Willebrand s disease the Pelger anomaly and hereditary spherocytosis (HS) show autosomal mode of inheritance (Wintrobe 1975 Britton 1974 Dacie 1960 Hardisty and Ingram 1965)

In each of these conditions Icelandic families have been studied who by genealogical information obtained indicate that the mutant genes causing these disorders and present in the investigated living family members has been transmitted through at least six genearations or 150-200 years The origin of these families has been traced to particular areas in Iceland The relationship of affected family members and their common geographical origin is considered to suggest that the same type of mutant gene is transmitted in these families Direct biochemical methods explaining the precise nature of the abnormality caused by these mutant genes are presently not available for any of the four hereditary conditions studied Therefore direct proof or disproof of the genetic homogeneity of the conditions under study is not possible

Ascertainment of the affected family members is based on morphological features of the blood cell mainly (in hereditary elliptocytosis Pelger anomaly and HS) and abnormal plasma coagulation factors in the case of von Willebrand s disease

Variants of each of these hereditary condition have been described by many workers indicating possible genetic heterogeneity The demonstration of genetic heterogeneity of hereditary elliptocytosis by linkage studies referred to previously is the only proof of genetic heterogeneity in the four hereditary conditions studied

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The Pelger anomaly was diagnosed in 1974 in an American woman married to an Icelander. One of their four children, a boy also has the anomaly

Von Willebrand's disease

Three families with vW are reviewed. They include 27 affected individuals, 17 males and 10 females. Severe symptoms of bleeding predominate in the males two of whom have died from haemorrhage. Typical lesions of hereditary haemorrhagic telangiectasia were found in one female who was considered to be a carrier of the v W gene

There is a reduced expressivity of the mutant gene, amounting to nonpenetrance mainly in the female members of the families. The clinical laboratory and hereditary findings in the v W families studied suggest much higher prevalence of the mutant v W gene than is indicated by clinically affected cases and cases ascertained by the laboratory tests used.

It is thought probable that the mutant gene present in the three families has originated from a common ancestor in a district which is common to the three families. Efforts to find relationship between them have been unsuccessful up to now

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from v W Ascertainment of asymptomatic v W family members with no or borderline changes in the coagulation bleeding tests would be important because such cases are among those who are prone to various hazards due to disease operations and drugs precipitating a bleeding episode By these recent immunological tests platelet aggregation test with ristocetin (Howard and Firkin, 1971 Weiss et al 1972, *ibidem*, 1973) and platelets adhesion tests to glass beads *It* has been possible to characterize genetic variants of v W (Holmberg and Nilsson (1972) and ibidem (1973) The riddle of v W *is still to* be solved and no single test or combination of tests are as yet available to *ascertain the* presence and type of gene or genes in every case

SUMMARY

Hereditary elliptocytosis

An Icelandic family with fifty elliptocytic *individuals is reviewed. Pedigree studies* indicate strongly that affected members of the family are descendants of a common *ancestor The hereditary pattern is typical of a dominant* autosomal gene with full penetrance A high incidence (over 57 per cent) of signs and/or symptoms of haemolysis *is found* among the affected at one time or another No haptoglobin was detected *in 80 per cent of affected individuals* investigated The age distribution of the affected at the time of diagnosis shows an increased incidence of anaemia with increasing age In three affected individuals splenectomy has been performed with satisfactory results The variation in the grades of haemolysis and the high incidence of haemolysis found in affected family members are discussed

Linkage analysis of 11 loci in 29 elliptocytic family units was done *Close linkage of the elliptocytosis locus with the acid* phosphate and Rhesus loci was excluded as was close linkage with other marker systems tested

Algerian-Icelandic family is *reviewed* in which the Algerian father had elliptocytosis as *did one of his two children.*

Hereditary spherocytosis (HS)

Thirty members with *typical HS* and *over* 70 apparently unaffected members belonging to 12 families have been studied. Splenectomy has been performed on 22 HS patients Of nine HS individuals who had *not under*gone surgical treatment in 1957 four suffered from severe anaemia presumably due to aplastic crisis associated with influenza. One of them died a male 18 years of age

Pedigree studies on one of the families indicate that the HS gene or genes have been transmitted through six generations over the past 200 years

Marked deficiency in the number of affected compared with the apparently unaffected members in the HS families is present. The most striking example of the uneven genetic ratio is a sibship of 15 members investigated haematologically with one member suffering from typical HS

Much reduced penetrance of the HS gene or the presence of the so-called mild form is upheld as the main explanation for the unevenness in the genetic ratio Pedigree studies and haematological observations made are considered to support this However *families* are also present in which abortions and *death* at an *early* age *indicated* that selection against the affected could also *disturb* the genetic ratio in *HS families*

The Pelger anomaly

An Icelandic family containing fourteen members with *Pelger anomaly is reviewed* It is possible that this family is the only one with this type of mutation in Icelanders. *No other Icelandic family has been found* (see below) by scanning blood films from over 40000 Icelanders mainly in the Reykja-

vik area. Genealogical information indicates that the Pelger anomaly gene has been present in this family over 200 years.

The Pelger anomaly was diagnosed in 1974 in an American woman married to an Icelander. One of their four children, a boy also has the anomaly.

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REFERENCES

Árnadóttir T (1951) Skutustaðaætt. Bókaútgáfa Pálmi H Jónsson Reykjavík

Austin, R F Desforges J F Hereditary Elliptocytosis An Unusual Presentation of Hemolysis in the Newborn Associated with Transient Morphologic Abnormalities Pediatrics *44* 196-200 1969

Bannerman R M., Renwick, J H The Hereditary Elliptocytosis Clinical and Linkage Data. Ann. Hum Genet., *26* 23-38 1962.

Bjarnason Ó., Bjarnason, V Edwards J H., *Fridriksson* S., Magnússon, M., Mourant, *A E Tills D The Blood Groups of Icelanders Ann Hum Genet. 36 425-458* 1973

Borchgrevink C F Egeberg O Pool G J *Skúlason T* Stormorken *H* Waaler *B* A Study of Cases of Congenital Hypo*prothrombinaemia.* Brit. J Haemat *5* 294 301 1959

Britton C J C Disorders of the Blood J and A. Churcill Ltd London, 1969

Burman D Congenital Spherocytosis in In fancy Arch Disease in Childhood *33* 335-*341* 1958

Buttersworth C E. Kracke R R Riser W A. Hereditary Spherocytic Anemia in the Negro Blood *9* 793-797 1950

Carruthers M F Mild Hereditary Spherocytosis — A Family Study Brit. med J *2* 1845-1847 1960

Dacie J V (1960) The Haemolytic Anaemias Congenital and Acquired 2nd edn., Part I The Congenital Anaemias Churcill London

Eyjólfsson G I Sigurbergsson K Telangiectasia hereditaria hemorrhagia Læknablaðið *59* 147 159 1973

Goodall H B Hendry D W W Lawler S D., Stephen S A.. Data on Linkage in Man Elliptocytosis and Blood Groups II Family 3 Ann Eugen, *17* 272 278 1953

Hardiatry R M., Ingram G I C Bleeding Disorders Blackwell *Sci* Publ., Oxford 1965

Howard M A., Firkin B G.. Ristocetin — A New Tool in the Investigation of Platelet Aggregation Thromb et Diath. Haemor., *26* 362 369 1971

Jacob Harry S.. The Abnormal Red-Cell Membrane in Hereditary Spherocytosis Evidence for the Causal Role of Mutant Microfilaments Brit J Haemat. 23 (Suppl) 35-44 1972.

Jacob H., *Amsden, T., White J..* Membrane Microfilaments of Erythrocytes Alteration *in* Intact Cells Reproduces the Hereditary Spherocytosis Syndrome Proc. Nat. Acad. Sci USA, *69 471-474 1972*

Jensson Ó Stefánsson M L., Dagbjartsson A. (unpublished 1976)

Jóhannsson E Ó.. The Pelger Anomaly Appelbergs Boktryckeri AB Uppsala 1963

Jónsson A K. Lögfræðingatal 1736-1963 Ísafoldarprentsmiðja h f Reykjavík, 1963.

Jónsson, E. Ættir Austfirðinga. Austfirðingafélagið í Reykjavík, Reykjavík 1953

Kaur J Catovsky D Valdemarsson, H Jensson Ó Spiers A. S D.. Familial Acute Myeloid Leukaemia with Acquired Pelger-Hüet Anomaly and Aneuploidy of C Group B Med J *4* 327 331 *1972.*

Kostinas J E., Cantow E. F., Wetze R A.. Autohaemolysis of cord blood in congenital spherocytosis and ABO incompatibility J Pediatrics *70* 273-276 1967

McKusick V A. Mendelian Inheritance in Man Catalogs of autosomal dominant autosomal recessive and x-linked phenotypes The John Hopkins Press Baltimore Sec. ed 1968

Magnusson B Ættir Síðupresta. Bókaútgáfan Norðri Reykjavík, 1960

Marshall R A Bird M Bailey H K Beckner E. Genetic linkage between ovalocytosis and the Rh blood type J Clin Invest. *33* 790-793 1954

Meulengracht E.. Der Chronische heredit äre hämolytische Ikterus Dr W Klink hardt Verlag Leipzig 1922.

Morton N E The Detection and Estimation of Linkage Between the Genes for Elliptocytosis and Rh Blood Type Amer J Hum Genet, *8* 80-96 1956

Nilsson, I M., Blombäck, M Blombäck, B.. v Willebrand s disease in Sweden Acta med. Scand *164* 263-278 1959

Nilsson I M Holmberg L Subtypes of Factor VIII Deficiencies. Transfusion and Immunology p 235-248 *1975 (Plenary*

Session Lectures of XIV Int. Congress of ISBT Helsinki, 1975) Vammala, 1975.

Oski, F A., Stockmann, J A., Anaemia in Early Infancy Annotation. Brit. J Haemat. 27 195, 1974

Quick, A. J., Hemorrhagic Diseases and the Pathology of Haemostasis Charles C Thomas. Publisher Springfield U.S.A., 1974

Race R R On the Inheritance and Linkage Relations of Acholuric Jaundice. Ann Eugen., 11 365-384, 1942.

Rizza, C R. Factor VIII — Related Antigen and von Willebrand's Disease Brit. J Haemat. 31 (Suppl.) 231-245 1975.

Stamey C C., Diamond, L K. Congenital Hemolytic Anaemia in the Newborn Amer J Dis. Child 94 616-622 1957

Stites D P Hershgold, E. J Perlman J D Fudenberg, H. H Factor VIII detection by hemagglutination inhibition hemophilia A and von Willebrand's disease. Science 171 196-197 1971

Young, L E., Izzo, M. J Platzer R F Hereditary Spherocytosis. Blood 6 1073-1098 1951

Weiss, H J Hoyer L W Rickles, F R., Warma, A., Rogers, J Quantitative assay of a plasma factor deficient in von Willebrand's disease that is neccessary of platelet aggregation J Clin Invest., 52, 2708-2716, 1973

Weiss H J Rogers, J Brand, H. Further Studies on the Von Willebrand Factor (Factor VIII) — Ristocetin — induced platelet aggregation. Abstract: Amer Soc of Hematology 15th Annual Meeting, Dec. 1972. Blood, 40 939 1972.

Wyandt, M S Bancroft, Paul, M Winship T O Elliptic Erythrocytes in Man, Arch. Intern Med. 68, 1043-1065 1941

Wintrobe, M M., Clinical Hematology Lea and Febiger Philadelphia, 1974

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REFERENCES

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Wyandt, M S., Bancroft, Paul, M Winship T O Elliptic Erythrocytes in Man, Arch. Intern. Med. 68, 1043-1065, 1941
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APPENDIX

List of papers in English Danish and Icelandic by the author and his co-authors

In English

Jensson, Ó Observations on the Leucocyte Blood Picture in Acute Uraemia. Brit. J Haemat., *4*, 422-427 1958.

Jensson, Ó Schade, R. O K. The Value of Alfa Chymotrypsin for Diagnostic Gastric Lavage. ACTA CYTOLOGIA, 6, 475-477 1962.

Jensson, Ó Jónasson, Th., Ólafsson, Ó Hereditary Elliptocytosis in Iceland. Brit. J Haemat., *13* 844-854 1967

Thorarinsson, A., Jensson, Ó Bjarnason, Ó Screening for Uterine Cancer in Iceland. Acta Cytologica *13* 304-308, 1969

Jensson, Ó Wallett, L. H. Von Willebrand s Disease in an Icelandic Family Acta med. Scand. *187* 229-234, 1970.

Jensson, Ó Survey of Human Genetics. 65° Icelandic Life Number 10, p. 23, 1970

Kaur J Catovsky D Valdemarsson, H., Jensson, Ó Spiers, A. S. D Familial Acute Myeloid Leukamia with Acquired Pelger Hüett Anomaly and Aneuploidy of C Group Brit. Med. J *4* 327-331, 1972.

Hauksdóttir H., Halldórsdóttir S Jensson, Ó *Mikkelsen, M., McDermott, A.* Pericentric Inversion of Chromosome No 13 in a Large Family Leading to Duplication Deficiency Causing Congenital Malformations in Three Individuals. J Med. Genet., *9* 413-421, 1972.

Árnason, A., Jensson, Ó Guðmundsson, S. Serum Esterases of Icelanders I. A silent Pseudocholinesterase Gene in an Icelandic Family Clin. Genet., 7 405-412, 1975.

Jensson, Ó Jónasson, J L., Magnússon, S. Studies on Hereditary Spherocytosis in Iceland. Acta Med. Scand. 201 187 195, 1977

Jensson, Ó Árnason, K., Jóhannesson, G M Úlfarsson, J Studies on the Pelger Anomaly in Iceland. Acta Med. Scand. 201 183-185, 1977

Guðmundsson, S. and Jensson, Ó Frequency of IgA deficiency in blood donors and Rh negative women in Iceland. Acta path. microbiol. scand. Sect. C, *85*.87-89, 1977

In Danish

Thorarinsson, A., Jensson, Ó Bjarnason, Ó. Masseundersögelser med henblik paa collum cancer Nord. Medicin, *78* 1608-1611, 1967

In Icelandic

Jensson, Ó Um magafrumurannsóknir Læknaneminn, *13* 3-10 1960

Jensson, Ó Árnason, K. Íslenzk Pelger fjölskylda. Læknablaðið, *49* 98-103, 1963.

Jensson, Ó., Ólafsson, Ó. Elliptocytosis hereditaria á Íslandi. Læknablaðið, *50* 195-164, 1964.

Jensson Ó Alsirak íslensk fjölskylda með arfgenga elliptocytosis. Læknablaðið, *51* 22 29, 1964

Jensson, Ó. Læknisfræðileg erfðafræði. Læknaneminn, *18* 5-14, 1965.

Þórarinsson, A., Jensson, Ó, Bjarnason, Ó., Krabbameinsleit hjá konum með fjölda rannsóknum. Læknablaðið *52* 145-157 1966

Jensson, Ó Júlíusson, B., Arnórsson, V Johnsen, B. Galli á D-litningahópi (13-15) Læknablaðið, *53* 229-238, 1967

Jensson, Ó Sitt af hverju um gagnsemi erfðafræðinnar Ljósmæðrablaðið, *46* 3-15, 1968.

Jensson, Ó Þorsteinsson, J Árdal, B. Fjölskyldur með von Willebrandssjúkdóm Læknablaðið, *56* 123-136, 1970.

Jensson, Ó Blóðbankastarfsemi og blóðgjafir Læknaneminn, *28* 56-61 1975.

Árnason, A., Jensson, Ó Guðmundsson, S. Öndunarlömun af vöðvaslappandi lyfi vegna arfgengs skorts á serum *cholinesterasa* Læknablaðið, *60* 15-19 1974

Jensson, Ó., Guðmundsson, S. Amerísk íslensk Pelger fjölskylda. Læknablaðið *60* 81-83, 1974.

Jensson, Ó Viðfangsefni nútíma blóðbanka Meinatæknirinn, p. 3-7 1973.

Jensson, Ó Bjarnason, Ó Frumugreining á *magakrabbameini. Læknablaðið, 61* 51 50 1975.

Jensson, Ó Jónsdóttir K. Stjarfi hjá blóðgjafa Læknaneminn, *28* 23-27 1975.

Jensson, Ó Bjarnason, Ó Hauksdóttir H Yfirlit um litningarannsóknir 1967 1973 Læknablaðið, *62* 127 130, 1976.

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FROM THE FIRST DEPARTMENT OF MEDICINE,
UNIVERSITY OF HELSINKI, AND FROM THE WIHURI
RESEARCH INSTITUTE, HELSINKI, FINLAND

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BY

SIRKKA KAUKOLA

HELSINKI 1978

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The incidence of coronary heart disease (CHD) has greatly increased throughout the world over the last 50 years up until recently CHD is the leading cause of death among males in western industrialized countries and the mortality among young and middle-aged men, particularly is high compared with that from other causes.

Coronary atherosclerosis is almost always responsible for CHD Little is known of the rate of progression of coronary atherosclerosis, but it seems to be variable (Vlodaver and Edwards 1971 Bemis et al. 1972, Kimbiris et al. 1974) At least 3/4 of the lumen of a major coronary artery must be occluded before blood flow becomes significantly disturbed (Hood 1971) Even then, collateral circulation may protect the area distal to the occlusion against ischemia. On the other hand, 5 to 15 per cent f patients display ischemic symptoms in the absence of verifiable obstructive disease (Proudfit et al. 1966, Welch et al 1970 and 1975 Friedberg 1972 and 1973, Day t al. 1977 Thompson et al 1977)

Many epidemiological studies have revealed several risk factors which increase susceptibility to CHD and accelerate the progression of coronary therosclerosis. However no causal relationship has been established between these factors and coronary atherosclerosis. The relative importance of these risk factors varies in different populations (Keys 1970 Dolder and Oliver 1974, Gertler and White 1976), but three major ones — hypertension, hyperlipidemia and heavy cigarette smoking — are effectively becoming universally accepted. Data from different studies show that each of these can increase the risk of premature coronary artery disease independently of the others (Epstein and Ostrander 1971 Keys et al. 1972, Kannel et al. 1976), though divergent opinions have also been put forward (Werkö 1976). Age, sex, and heredity are important risk factors for ischemic heart disease in all populations. In addition, at least 40 minor risk factors have been described in the literature (Stamler et al. 1972, Fejfar 1973, Blackburn 1974), though their relative importance in CHD remains small or contradictory Examples of minor isk factors are abnormal glucose tolerance, obesity sedentary life style and psychosocial factors, while still others are being found. Generally the impact of risk factors is viewed as additive.

As a disease of unknown pathogenesis and etiology coronary atherosclerosis remains an enigma. Some pathological evidence appears to favor the view that factors or changes related to the connective tissue of the arterial wall might play a role in the development of occlusive lesions (Cardinale and Udenfriend 1974 Ooshima et al. 1975 and 1977 Fuller et al. 1976, Prockop et al. 1976). If so it is possible that the connective tissue disorder is universal and therefore likely to be detectable elsewhere in the body as well. Observations to support this are very scare indeed, being

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limited to a few equivocal clinical observa tions.

Certain extracardiac signs have been con sidered to be associated with the presence of CHD or its clinical consequences. Myocardial infarction has been suggested to initiate the development of Dupuytren s contracture (Ask Upmark 1969) but its specificity as a sign of CHD is very low During the 1970 s it has become apparent that a diagonal ear-lobe crease (EC) could be a sign of CHD Investigations to clarify this possible relationship and its specificity and sensitivity are still few in number however and the opinions thus generated have been contradictory

The following literature survey summarizes the published evidence concerning the relationship between EC and ischemic heart disease.

SURVEY OF THE LITERATURE

Frank (1973) was first to describe a prominent crease in the lobule portion of the auricle and call it a positive ear-lobe sign. He studied 20 patients aged 60 years or less with this sign in terms of personal and family histories of premature cardiovascular disease and known risk factors. All but one displayed 1 or more of 6 possible risk factors, viz. hypercholesterolemia, hypertriglyceridemia, abnormal glucose tolerance, hypertension, cigarette smoking and a family history of premature cardiovascular disease. Two patients had angina and a third patient's electrocardiogram indicated ischemia. Frank suggested that the positive ear lobe sign was associated with premature cardiovascular disease.

The crease was later re-named the diagonal ear lobe crease (Lichstein et al. 1974), a term which has been in common use ever since. Lichstein et al. examined 531 patients with acute myocardial infarction over a three-year period. The age range was from 30 to 89 years, but no details of the patient selection were reported. Two hundred and fifty-one patients (47) exhibited EC, whereas it was present in only 92 (30) of 303 age-matched control patients with no clinical evidence of CHD. In the CHD group the prevalence of diabetes mellitus and hypertension was similar in those with and without EC. Smoking in patients with CHD and EC was significantly more common than in those with CHD but without EC, although no significant difference was found in the prevalence of smoking in the control group with or without EC. These workers regarded EC as a coronary risk factor with an increasing prevalence between the sixth and ninth decades. They suggested that EC is not present at birth but develops later in life, the mechanism remaining to be clarified.

To determine the possible relationship between EC and CHD Sternlieb et al. (1974) undertook a study of 144 unselected patients in whom the presence or absence of coronary artery disease was verified by coronary arteriography. One hundred and twenty (90 %) of the 133 patients with EC had CHD whereas 10 of the 11 (91 %) without EC had normal coronary arteries.

In another study on 211 consecutive patients undergoing coronary arteriography the relationship of EC and CHD was examined (Mehta and Hamby 1974). One hundred and fifty-nine of the 211 patients had CHD while 52 had normal coronary arteries. No statistically significant difference was present between the frequency of EC in patients with CHD (58) and those with normal coronary arteries (60 %). The only correlation was between the frequency of EC and advancing age: it was present in 34 % of the patients below 55 years and in 65 % of those above.

Christiansen et al. (1975) agreed with Mehta and Hamby (1974) that the prevalence of EC increases with age. Their results also supported the findings of Lichstein et al. (1974) that the presence of EC was positively correlated with CHD. In this study (Christiansen

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OBJECTS OF THE PRESENT STUDY

The ear lobe crease (EC) is an easily detectable sign which might be useful in the diagnosis of CHD, although its clinical significance has not been established. The purpose of the present study was.

- to examine whether a statistical correlation exists between EC and CHD
- to determine whether there is a statistical relationship between EC and the major and some minor coronary risk factors, viz. hypertension, hyperlipidemia, cigarette smoking, diabetes, obesity and sedentary living; also taking into account heredity and blood group, and factors such as other cardiovascular disease, birthplace and drug treatment (especially with beta-blockers).
- to evaluate the developmental features of EC.

et al.) a closer relationship was found between CHD and EC than between CHD and the risk factors of arterial hypertension, cigarette smoking and diabetes mellitus.

A significant positive correlation between EC and diabetic retinopathy was found by Andresen et al. (1976) who examined 101 diabetic patients EC was seen in 51 4 % of the patients with retinopathy (mean age 53.9 ± 13.8 years) but in only 7 6 % of those with normal retinal vessels (mean age 52.7 ± 13.7 years) They considered this observation to indicate a correlation between EC and generalized angiopathy

The data of Sprague (1976) suggest that intraoperative cardiovascular complications occur more frequently in patients with EC. The prevalence of postoperative complications was also greater in those with this sign. EC was regarded to be associated with CHD and to become more common with each decade above the third.

The frequency of EC and the extent and severity of coronary atherosclerosis have been compared in one postmortem study (Lichstein et al. 1976) The investigation involved 113 consecutive autopsies on patients aged 40 years or over comprising 32 patients without EC, 22 with unilateral EC, and 59 with bilateral EC The extent of sclerosis of the coronary arteries was more severe in those with bilateral EC than in those without EC the difference being statistically significant. However it was not significantly differ between those with unilateral EC and th without EC. The degree of occlusion did r differ significantly between the groups.

Doering et al. (1977) examined 50 patie with CHD of any type and 38 control patie in the age range 30 to 80 The groups we not age-matched, but 18 pairs of patie were matched with regard to age, sex, a CHD or control information. The prevalen of EC was 88 0 % in all CHD patients a 36.8 % in the controls, and in the age- a sex matched groups 94 4 % and 44 4 %, r spectively

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MATERIAL AND METHODS

The clinical study was made in two parts. In the first, patients with acute myocardial infarction were compared with an age- and sex matched control group. In the second part, patients with anginal symptoms who had been examined by coronary angiography were studied. They were divided into two groups those with CHD and those with normal coronary arteries

PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (AMI)

The group comprised 219 patients surviving acute myocardial infarction (AMI) who were admitted to the First, Second, and Third Departments of Medicine Helsinki University Central Hospital, from March through May and from September through November 1976 There were 165 men aged 32 to 65 years and 54 women aged 43 to 65 with AMI (AMI patients, Table 1) fulfilling the criteria of WHO (Working Group of Ischaemic Heart Disease Registers, EURO 8201 (5) 1971). Patients aged 65 years or over were excluded. During the period of collection of the patient material a total of 288 patients under 65 and with AMI were admitted to this hospital. Thus the patient sample involved about 76 % of all the survivors of AMI hospitalized and, although strictly neither a consecutive nor random patient sample it is probably fairly representative.

Table 1 Age and sex distributions of patients with acute myocardial infarction

Sex	Age in years				
	30—39	40—49	50—59	60—65	Total
Males	10	46	68	41	165
Females	—	11	24	19	54
Total	10	57	92	60	219

After admission, any history of chest pain was enquired about and serial electrocardiographic recordings and enzyme determinations were made as necessary The serum enzyme most commonly determined was serum glutamine oxalacetic transaminase (S-ASAT) and, occasionally serum creatine phosphokinase (S-CK) Serum levels were regarded as elevated if ASAT was 40 U/l or above and CK 50 U/l or above According to the extent of heart injury myocardial infarctions were divided into subendocardial and transmural infarctions on the basis of WHO criteria. AMI could be the first or a recurrent event, but the same patient was not included more than once

The patients were examined by the author for the presence or absence of EC and personal interview was used to obtain the following data family history of premature cardiovascular disease and diabetes birth place father s and mother s birthplaces previous angina pectoris and myoc in-

farction, arterial hypertension, other cardiovascular disease, diabetes, smoking habits, physical activity at work and during leisure time, and previous drug treatment. Body weight and height were recorded. Fasting blood glucose and serum cholesterol and triglyceride values were determined about two months after the acute attack to obviate the changes known to occur in these variables during the acute period of myocardial infarction (Welin 1946, Blörck et al. 1957 Miettinen 1957 Dodds and Mills 1959 Sowton 1962, Nicolaysen and Westlund 1963, Allison et al. 1969). Values from earlier records were used for these criteria if the patients did not return for examination after this myocardial infarction attack. Blood group had been determined on the wards in most cases.

CONTROL SUBJECTS

The control group consisted of 290 subjects (236 men and 54 women) working for the State Railways in the Helsinki area. Selection began by all the railway employees working as clerks, guards and switchmen in the Helsinki area being classified by sex, age and occupation. From each occupational group 100 subjects were drawn so that their ge distribution corresponded to that of the AMI cases in the Helsinki area. The method of forming the control group has been described in detail earlier (Romo 1972).

The examination was carried out at the Railw y Health Centre, Helsinki, during August and September 1976 as follows. every subject received a questionnaire concerning the same data as the patients with AMI were asked about. The data in the completed forms were checked in a later interview The presence or absence of EC was noted and the electrocardiogram, blood pressure, body weight and height were recorded. Determinations f fasting blood glucose, serum cholesterol and triglycerides were made at the Department of Clinical Chemistry Helsinki University Central Hospital. After this the final control group was formed excluding the 10 subjects with previous myocardial infarction or abnormal Q-waves or ST-segment and T wave abnormalities in the resting electrocardiogram according to the criteria of the Minnesota code (Rose and Blackburn 1968).

In the final group men were distributed approximately equally as clerks, guards or switchmen, while all women were clerks. Table 2 gives their age distributions. The age of men ranged from 32 to 63 years, but there were only 5 men over 59 years due to the early retirement age of railway employees in most jobs. The male control group was therefore well age-matched with the male infarction group only up to 59 years, the mean age of the younger than this being 50 years. Female subjects ranged from 43 to 65 years, with a mean of 57 The female control group was well age-matched with the female infarction patients.

T ble 2 *Age and sex distributions of control subjects*

Sex	Age in years				
	30—39	40—49	50—59	60—65	Total
Males	13	87	131	5	236
Females	—	12	24	18	54
Total	13	99	155	23	290

PATIENTS STUDIED BY CORONARY ANGIOGRAPHY

Two hundred and eighty-six patients studied by coronary angiography at the Department of Diagnostic Radiology Helsinki University Central Hospital, made up this group. The

study was carried out from March, 1976 to April, 1977 One hundred and two consecutive patients were examined when they came to hospital for coronary angiography or coronary by pass surgery The other 184 patients were invited for examination in March and April, 1977 These patients were living in the Helsinki area and were selected from those having had coronary angiography in 1971—76 and who were willing to cooperate. Thus the patient group as a whole should be considered as a selected one.

Coronary angiography had been performed on the patients because of angina pectoris or atypical angina pectoris or unexplained ischemic electrocardiographic changes in a bicycle ergometer test. The angiography was selective in 280 cases, while a semi-selective technique was used for 6 others. The findings were analyzed by two experienced radiologists. Otherwise, the same data were collected from these patients as mentioned earlier In addition determinations of serum total lipids and lipoprotein electrophoresis on agarose gel were performed. Hyperlipoproteinemias were divided into subgroups based on WHO recommendation (Beaumont et al. 1970) Further attention was paid to serum alpha lipoprotein or high density lipoprotein (HDL) the level of which has been found to be low in patients with CHD (Nikkilä 1953 Lewis et al. 1974 Miller and Miller 1975 Berg et al. 1976)

The patients studied by coronary angiography were divided into subgroups according to the extent of coronary artery disease. Each individual coronary artery was evaluated by assessing the extent of coronary atherosclerosis present. Particular attention was focused on the right coronary artery (RCA), the left main coronary artery (LCA) the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCX) If the degree of stenosis was 50 % or more in at least one of these coronary

Table 3 Age and sex distributions of CH patients

Sex	Age in years					
	20—29	30—39	40—49	50—59	60—66	To
Males	1	20	68	72	13	17
Females	—	7	10	8	1	2
Total	1	27	78	80	14	20

arteries, there was considered to be singl double, or triple vessel disease according t the number of arteries affected. Significa coronary atherosclerosis was found in 20 patients (CHD patients, Table 3) i.e. 50 wit single vessel disease, 66 with double vesse disease and 84 with triple vessel disease. Th other group consisted of 86 patients with n significant atherosclerotic changes in corona ry arteries (non-CHD patients, Table 4). Som

Table 4 Age and sex distributions of non-CH patients

Sex	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Males	2	9	15	8	1	35
Females	—	8	24	17	2	51
Total	2	17	39	25	3	86

insignificant involvement (occlusion less than 50 %) was found in 11 cases and two investigations revealed a hypoplastic RCA, while 73 cases had fully normal coronary arteriogram.

The CHD group consisted of 174 men aged 26—66 and 26 women aged 30—66 The mean age was 48 years for both sexes In the non CHD group were 35 men and 51 women, the age range for men being from 6 to 60 years and for women from 32 to 66 years. The mean age was 51 years for both sexes.



Fig 1 A typical diagonal ear lobe crease in the lobule of the uricle

DEFINITIONS

The diagonal ear-lobe crease

The sign is clearly discernable as a downwards oblique crease in the lobule of the auricle (Fig 1).

In this study the patients were examined for the presence o absence of EC, and if present the sign was recorded as either bilateral or unilateral. Only a clear-cut crease was accepted as a positive finding. The examination was performed by the author in all cases. To confirm the reliability of this investigation a material of 500 unselected subjects was examined by an ex perienced internist and by the author independently The difference was 2.5 /o.

Assessment of smoking habits

The patients and subjects were divided into smokers, ex-smokers and non-smokers as follows. a smoker was defined as a person who smoked at least one cigarette a day Smokers were further divided into subgroups

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Table 3 Age and sex distributions of CHD patients

Sex	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Males	1	20	68	72	13	174
Females	—	7	10	8	1	26
Total	1	27	78	80	14	200

arteries, there was considered to be single double, or triple vessel disease according to the number of arteries affected Significant coronary atherosclerosis was found in 200 patients (CHD patients, Table 3) i.e. 50 with single vessel disease, 66 with double vessel disease and 84 with triple vessel disease. The other group consisted of 86 patients with no significant atherosclerotic changes in coronary arteries (non-CHD patients, Table 4) Some

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Sex	Age in years					
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Assesment of obesity

Body weight and height were used to calculate the relative body weight using Quetlett's formula $\frac{\text{weight (kg)}}{\text{height (cm)}^2} \times 100$ (Khosla and Lowe 1967). A relative body weight of 0 28 was regarded as the limit for obesity

Assessment of physical activity

Physical activity both at work and during leisure time was enquired of the AMI patients and the control group Attention was paid to the daily duration of sitting standing and walking and to the lifting and carrying of heavy objects when standing and walking

Classification was accomplished according to the following definitions (Saltin and Grimby 1968 Wilhelmsen et al. 1971)

Activity at work

Group I (inactive) Mainly sitting
Group II (medium) Most of the time spent standing or walking Rarely lifting or carrying heavy objects.
Group III (active) Much walking possibly also climbing stairs. Occasionally lifting or carrying heavy objects.
Group IV (very active) Frequent lifting or carrying heavy objects in addition to much walking

Leisure activity

Group I (inactive) No physical activity during leisure time.
Group II (medium) Walking, cycling, fishing [illegible]
Group III (active) Regular sporting activit[illegible] or heavy gardening or physical work at hom[illegible] for at least 2—3 hours weekly
Group IV (very active) Much sportin[illegible] activity many times weekly

Birthplace

Due to the varying incidence of CHD i[illegible] different regions of Finland (Keys 1970) th[illegible] birthplace was taken into account. Th[illegible] inhabitants of western and eastern Finlan[illegible] may also differ genetically (Kajanoja 1971) However coronary atherosclerosis seems t[illegible] develop to the same extent in individuals o[illegible] both populations (Rissanen 1974) On the basi[illegible] of these studies the country was divided into

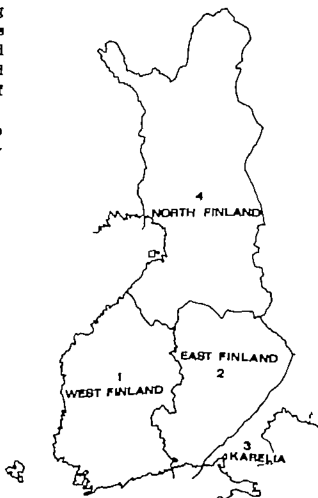


Fig The country divided into three regi[illegible] coding the patients nd subjects into groups by [illegible]

3 regions — west Finland, east Finland, and north Finland — and a fourth was former Finnish Karelia — the area from which people were resettled in other parts of Finland after World War II (Fig. 2).

STATISTICAL METHODS

Student's t-test and the chi square test were used in estimating the differences between the means.

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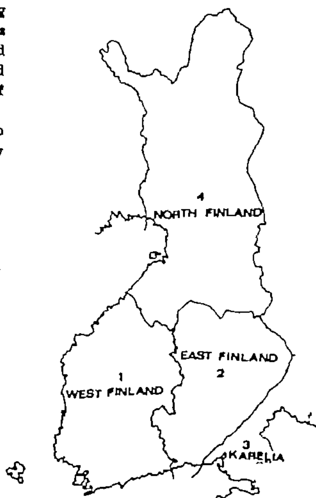
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Leisure activity

Group I (inactive) No physical activity during leisure time.
Group II (medium) Walking cycling fishing moderate gardening or physical work at home for at least 4 hours weekly
Group III (active) Regular sporting acti or heavy gardening or physical work at h for at least 2—3 hours weekly
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RESULTS

A. PATIENTS WITH MYOCARDIAL INFARCTION AND CONTROL SUBJECTS

PREVALENCE OF THE DIAGONAL EAR LOBE CREASE

Patients with myocardial infarction

EC was found in 151 of 219 AMI patients (69 %) The frequency was the same (69 %) in both men and women (Table 5) The pre valence of EC among the youngest AMI patients was remarkable — seven of the 10 male patients (70 %) aged 30—39 years had EC. The increasing prevalence with age was not statistically significant. The youngest man with EC was 32 years and the youngest woman 43 They were also the youngest AMI patients of either sex.

EC was more often bilateral than unilateral at all ages However the unilateral EC was fairly common in men up to 49 years of age In women it was more frequently unilateral than bilateral up to 59 years.

Control subjects

EC was present in 71 of 290 subjects (24 %). The sign was found in 66 of 236 men (28 %) while only 5 women (9 %) had it (Table 6) The prevalence did not show a statistically significant increase with age in these groups. Only one man under 40 had the sign, and in women it was not found in those under 54 years. The youngest man with EC was 35 years of age and the youngest woman 57 whereas the youngest man and woman in the whole control group were 32 and 43 respectively

Both the unilateral and bilateral EC were found fairly equally among those subjects

Table 5 Percentage of AMI patients hav ng the ea lobe crease by age and s x Figures pa theses indicate proportions of tot l gro ps

Sex	Age in years				
	30—39	40—49	50—59	60—65	Total
Males	0 (7/10)	61 (28 46)	71 (48 68)	6 (21 41	69 114 165
Females	—	46 (5 11)	71 (17 24)	79 (15, 19)	69 (37 54
Total	0 (7 10)	58 (33 57)	71 (65, 92)	77 (46 60)	69 (151

Table 6. Percentage of control subjects having the ear-lobe crease by age and sex. Figures in parentheses indicate proportions of total groups

Sex	Age in years				
	30—39	40—49	50—59	60—65	Total
Males	8 (1/13)	24 (21/87)	31 (41/131)	— (3/5)	28 (66/236)
Females	—	— (—/12)	12 (3/24)	11 (2/18)	9 (5/54)
Total	8 (1/13)	21 (21/99)	28 (44/155)	22 (5/23)	24 (71/290)

aged 40—49 years, but the bilateral EC was more common in men aged 50 or over. In women EC was seen so infrequently that comparison in this respect is impossible.

Patients with myocardial infarction compared to control subjects

The prevalence of EC was 69 % in the AMI patients and 24 % in the control subjects. The corresponding percentages were 66 and 25 in those below 60 years of age, where the groups were well age-matched and thus fully comparable. These differences were significant ($p < 0.01$) for the age group 30—39 years and highly significant ($p < 0.001$) for the other groups (Fig. 3).

PREVALENCE OF CORONARY RISK FACTORS IN PATIENTS WITH MYOCARDIAL INFARCTION AND CONTROL SUBJECTS

The AMI and control groups were adequately age-matched between 30 and 59 years of age and thus the prevalences of coronary risk factors in patients and controls were compared in this age range only. The former group comprised 189 patients and the latter 267 subjects.

History of arterial hypertension

A history of hypertension was revealed by 57 AMI patients (36) 35 % of men and 48 % of women. The highest prevalence was found in the 40 to 49 year age group in both men (35) and women (55 %) but then the frequency decreased with age, being clearly higher in women than in men for all age groups.

In the control group hypertension had been previously diagnosed in 55 subjects (19 %). The prevalence was the same for men and women. None of the women under 50 years had hypertension. However men had an

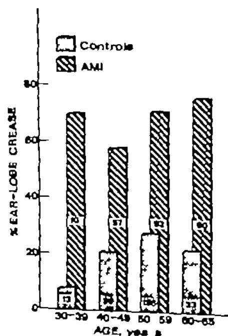


Fig. 3. Prevalence of the ear-lobe crease in AMI patients and controls by age. The numbers in the columns indicate the numbers of all individuals in each group.

RESULTS

A. PATIENTS WITH MYOCARDIAL INFARCTION AND CONTROL SUBJECTS

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EC was present in 71 of 290 subjects (24 %) The sign was found in 66 of 236 men (28 %) while only 5 women (9 %) had it (Table 6) *The prevalence did not show a statistically* significant increase with age in these groups. Only one man under 40 had the sign, and in women it was not found in those under 50 years The youngest man with EC was 38 years of age and the youngest woman 57 whereas the youngest man and woman in the whole control group were 32 and 43 respectively

Both the unilateral and bilateral EC were found fairly equally among those subjects

Table 5 Percentage of AMI patients having the ea lobe crease by age a d sex F gures n pa enth es dicate proportions of total groups

Sex	Age in years				Total
	30—39	40—49	50—59	60—65	
Males	70 (7/10)	61 (28/46)	71 (48/68)	6 (31/41)	69 (114/165)
Females	—	46 (5/11)	71 (17/24)	79 (15/19)	69 (37/54)
Total	70 (7/10)	58 (33/57)	71 (65/92)	77 (46/60)	69 (151/219)

ble 8. Mean relative body weights in AMI pa-
its and control subjects

x	AMI patients		Control subjects		
	Mean	S.D.	Mean	S.D.	p
lales	0.241	0.033	0.250	0.030	N.S.
emales	0.249	0.033	0.253	0.042	N.S.
'otal	0.234	0.033	0.258	0.033	N.S.

valence being 54.5 % for men and 75.5 % for women. In the control group the corresponding percentages were 32 %, 30 % and 43 %. The differences were highly significant ($p < 0.001$).

The prevalence of history of hypertension in the families of AMI patients was 30 %, being again higher in women (38 %) than in men (28 %). 43 % of control subjects had hypertension in the family and the proportion was the same for both sexes. The difference between the groups was almost significant ($p < 0.05$).

With regard to history of diabetes in the family positive answers were given by 19 % of AMI patients, 21 % of men and 18 % of women. The corresponding proportions were 25 %, 25 % and 28 % in the control group. In this case the differences were not significant.

The birthplace of the AMI patients and their parents was very often the same, and the situation was similar in the control group. There were no statistically significant differences between the groups here, either.

THE DIAGONAL EAR LOBE CREASE AND CORONARY RISK FACTORS

The relationship between EC and coronary risk factors was studied in AMI patients and control subjects separately. Both groups were divided into those with EC, either bilaterally or unilaterally (EC patients and subjects) and those without EC (NEC patients and subjects).

Coronary risk factors in AMI patients with and without the ear lobe crease

The distribution of the AMI group as EC and NEC patients in different age groups is shown in Table 9.

History of arterial hypertension

The prevalence of hypertension was 34 % in the EC and 38 % in the NEC patients, which was not a statistically significant difference and neither were those for different age groups.

Serum lipids

Serum cholesterol

The mean serum cholesterol of the EC patients was 7.7 ± 1.6 mmol/l (mean ± S.D.), whereas in the NEC patients it was 7.2 ± 1.4 mmol/l. The same trend was noted in different age groups except in those over 60 years (Fig. 4). The differences were statistically non-significant.

Table 9. AMI patients classified as those with (EC) or without (NEC) the ear-lobe crease by age. Figures in parentheses indicate percentages

Group	Age in years				
	30—39	40—49	50—59	60—65	Total
EC	7 (70)	33 (58)	65 (71)	46 (76)	151 (69)
NEC	3 (30)	24 (42)	27 (29)	14 (23)	68 (31)

Table 7 Mean serum cholesterol and triglyceride va ues in AMI patients and control subjects

Sex	AMI patients			Control subjects			p
	N	mmol/l	S.D	N	mmol/l	S.D	
Serum cholesterol							
Males	130	7.5	1 4	236	7 0	1.2	< [illegible]
Females	45	7 7	1.9	54	7.2	1.3	< 0[illegible]
Total	175	7.5	1.6	290	7 0	1.2	< 0[illegible]
Serum triglycerides							
Males	128	2.30	1 15	235	1.68	1.09	< 0.0[illegible]
Females	41	2.18	2.55	54	1 64	1 16	< 0.0[illegible]
Total	169	2.27	1.60	289	1.28	0.65	< [illegible]

equal prevalence of hypertension in all age groups over 40 years.

The difference in the prevalence of hyper tension between the total patient and control groups was statistically highly significant ($p < 0\ 001$)

Serum lipids

Table 7 presents the mean serum cholesterol and triglyceride concentrations for both AMI and control subjects indicating also the sig nificance of the differences between the groups.

Smoking

Among AMI patients 53 % were current smokers and 27 % ex smokers. Consumption of 20 cigarettes a day or more was the most common habit (34 %) All 10 patients under 40 years of age were currently smokers, 9 of them using more than 20 cigarettes a day 38 % of men and 20 % of women consumed more than 20 cigarettes a day Less than 20 cigarettes a day were smoked by 16.5 % of patients and cigars or a pipe by 3 %. 14 % of men and 39 % of women were non smokers.

In the control group there were 31 % current smokers, 39 % ex smokers and 31 % non-smokers. Only 4 % of women and 14 of men smoked 20 cigarettes or more a day while 20 % of women and 15 % of men smoked under 20 cigarettes a day A pipe or cigars were smoked by only 2.4 % of this group A considerable proportion of men (45 %) had given up smoking and most women (67 %) had never smoked.

The differences in smoking habits between the total patient and control groups were statistically highly significant ($p < 0\ 001$).

Diabetes mellitus

Diabetes had been previously diagnosed i 21.5 % of AMI patients and fasting bloo glucose exceeded 5.3 mmol/l in a further of 205 patients (2 4 %) In the control grou diabetes prevailed in only 4.5 % of subject and fasting blood glucose was elevated in a further 8 of 231 subjects (3.5 %) The dif ference was statistically highly significant ($p < 0.001$)

Obesity

The mean relative body weights of the AMI and control groups are presented in Table 8.

Family history of premature cardiovascular disease and diabetes. Birthplace

Premature CHD was reported to have oc curred in the family (i.e. parents brothers and sisters) by 130 patients (60) the pre-

Table 8. Mean relative body weights i AMI patients and control subjects

Sex	AMI patients		Control subjects		p
	Mean	S.D	Mean	S.D	
Males	0.261	0.035	0.259	0.036	N.S.
Females	0.248	[illegible]	0.253	0.042	N.S.
Total	0.256	[illegible]	0.258	[illegible]	N.S.

valence being 54.5 % for men and 75.5 / for women. In the control group the corresponding percentages were 32 /, 30 / and 43 /. The differences were highly significant ($p < 0.001$).

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NEC	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

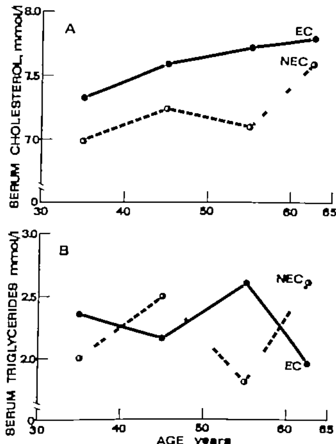


Fig. 4 Mean serum cholesterol (A) and triglycerides (B) of EC and NEC patients in the AMI group.

Serum triglycerides

Mean serum triglycerides were above the normal range in all age groups of both EC and NEC patients (Fig 4) The mean of the EC patients was 2.32 ± 1 78 mmol/l and that of the NEC patients 2 18 ± 1 71 mmol/L The differences were not statistically significant.

Smoking

The EC patients were less frequently current smokers (52 %) and ex smokers (25 %) than the NEC patients (56 % and 29 %). Non-smokers represented 23 % of the EC patients and 15 % of the NEC patients. The differences in daily consumption of cigarettes between these groups were small (Table 10), and none were statistically significant.

Diabetes mellitus

The prevalence of diabetes was 22 % in the EC and 21 % in the NEC patients (p NS).

Obesity

The mean relative body weight was 0.254 ± 0 037 in the EC and 0.257 ± 0 028 in the NEC patients. This difference was not statistically significant and neither were the means in different age groups (Fig 5)

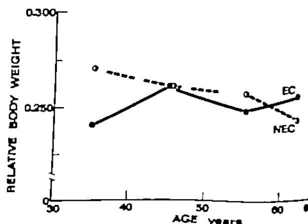


Fig. 5 Mean relative body weight of EC and NEC patients in the AMI group.

Level of physical activity

Fig 6 presents the distribution of the EC and NEC patients according to physical activity

Table 10 Distribution of EC and NEC patients in the AMI group by smoking habit Figures in parentheses indicate percentages

Group	Current cigarette smoking < 20 per day	Current cigarette smoking ≥ 20 per day	Cigar/pipe	Ex smokers	Non-smokers	Total
EC	26 (17)	49 (33)	3 (2)	38 (25)	34 (23)	150
NEC	10 (15)	25 (37)	3 (4)	20 (29)	10 (15)	68

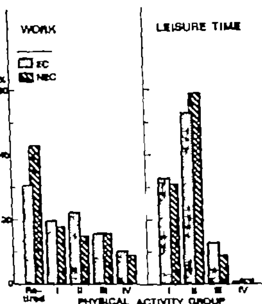


Fig 6 Distribution of EC and NEC patients in the AMI group according to level of the physical activity at work and during leisure time

at work. They were dispersed fairly similarly throughout all four activity groups (p NS) 31 of the EC patients and 43 % of the NEC patients were retired.

The physical activity during leisure time did not differ significantly between the EC and NEC groups. The distribution into four leisure activity level groups is shown in Fig 6

Blood group

The EC and NEC patients were distributed fairly similarly among the different blood groups A 42 and 54 %, B 16 / and 19 %, AB 11 and 4 %, O 20 and 23 %, respectively (p NS)

Family history of premature cardiovascular disease and diabetes. Birthplace

Premature CHD in the family was reported by 59 of the EC and 61 / of the NEC patients (p NS).

A history of hypertension was considerably more frequent in the families of the NEC patients (43 %) than in those of the EC patients (24 %). This difference was statistically significant ($p < 0.01$).

Diabetes was equally represented in family histories of the EC (19 %) and NEC patients (18.5 %), without a statistically significant difference.

A relatively greater proportion of the NEC patients (58) and their parents (54 %) were born in eastern Finland compared to the EC patients (50 %) and their parents (48 % and 46 %). The situation was opposite for western Finland. With regard to Karelia the percentages were very similar in both groups (Fig 7). None of the differences was statistically significant.

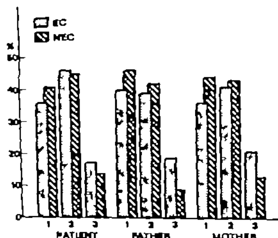


Fig. 7 Distribution of EC and NEC patients and their parents in the AMI group according to birthplace (1. west Finland, 2. east Finland, 3. Karelia).

Other characteristics of AMI patients with and without the ear-lobe crease

Previous and current history of CHD

The duration of angina pectoris had been fairly similar (p NS) in both groups. The EC patients had experienced symptoms for 2.3 ± 3.7 years and the NEC patients for 2.6 ± 3.5 years prior to this study

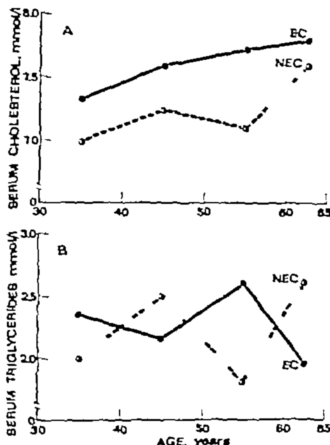


Fig 4 Mean serum cholesterol (A) and triglycerides (B) of EC and NEC patients in the AMI group.

Serum triglycerides

Mean serum triglycerides were above the normal range in all age groups of both EC and NEC patients (Fig 4) The mean of the EC patients was 2.3_ ± 1 ⁻8 mmol l and that of the NEC patients 2.18 ± 1.21 mmol/l. The differences were not statistically significant.

Smoking

The EC patients were less frequently current smokers (52) and ex smokers (25 %) than the NEC patients (56 % and 29). Non-smokers represented _3 of the EC patients and 15 % of the NEC patients. The differences in daily consumption of cigarettes between these groups were small (Table 10) and none were statistically significant.

Diabetes mellitus

The prevalence of diabetes was __ % in the EC and 21 % in the NEC patients (p NS)

Obesity

The mean relative body weight was 0._54 ± 0 037 in the EC and 0.257 ± 0 0_8 in the NEC patients. This difference was not statistically significant and neither were the means in different age groups (Fig 5).

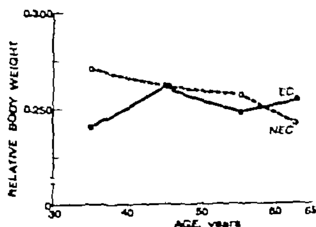


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Level of physical activity

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Group	Current cigarette smoking < _0 per day	Current cigarette smoking ≥ 20 per day	Cigar pipe	Ex smokers	Non smokers	Total
EC	8 (1⁻)	49 (33)	3 (2)	28 (_5)	34 (_	50
NEC	10 (15)	_5 (3⁻)	3 (4)	9 (_9)	10 1	64

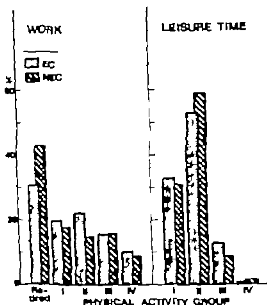


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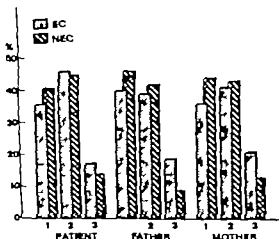


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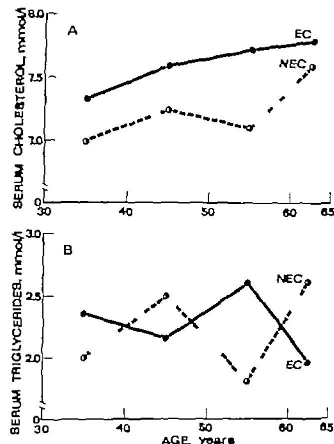


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Mean serum triglycerides were above the normal range in all age groups of both EC and NEC patients (Fig 4) The mean of the EC patients was 2.32 ± 1 78 mmol/l and that of the NEC patients 2.18 ± 1.21 mmol/l. The differences were not statistically significant.

Smoking

The EC patients were less frequently current smokers (52 %) and ex-smokers (25 %) than the NEC patients (56 % and 29 %) Non smokers represented 23 % of the EC patients and 15 % of the NEC patients. The differences in daily consumption of cigarettes between these groups were small (Table 10), and none were statistically significant.

Diabetes mellitus

The prevalence of diabetes was 22 % in the EC and 21 % in the NEC patients (p NS)

Obesity

The mean relative body weight was 0 254 ± 0 037 in the EC and 0.257 ± 0 028 in the NEC patients. This difference was not statistically significant and neither were the means in different age groups (Fig 5).

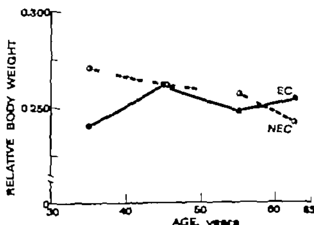


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NEC	10 (15)	25 (37)	3 (4)	20 (29)	10 (15)	68

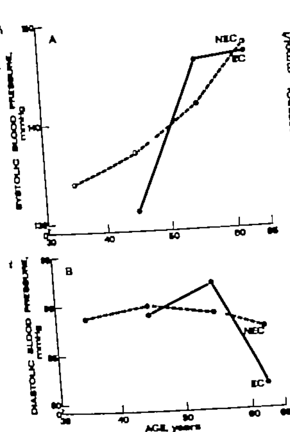


Fig 8 Mean systolic (A) and diastolic (B) blood pressure of EC and NEC controls.

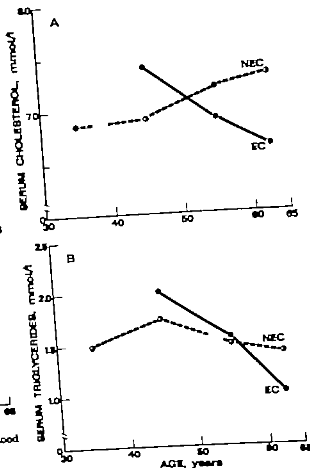


Fig 9 Mean serum cholesterol (A) and triglycerides (B) of EC and NEC controls.

Diastolic blood pressure

The mean diastolic blood pressure differed only slightly between the EC and NEC groups It was 90 ± 10 mmHg in the former and 89 ± 11 mmHg in the latter The differences were also small in the different age groups (Fig 8) without any statistical significance.

Serum lipids

S rum chole t rol

The mean serum cholesterol did n t deviate significantly between the EC and NEC control subjects. The means were 7.0 ± 1.2 mmol/l and 7 1 ± 1.2 mmol/l, and those by ge groups are indicated in Fig 9

Serum triglycerides

No significant difference could be found with respect to serum triglycerides in this comparison either The means were 1.62 ± 1.24 mmol/l for the EC subjects and 1.56 ± 1.04 mmol/l for the NEC subjects, and the means by age groups were quite close to these (Fig. 9)

Smoking

Among controls the EC subjects were less frequently current smokers (22.5) and non-smokers (28) than the NEC subjects (32 /)

The NEC patients seemed to have a trend of more previous myocardial infarctions (38 %) than the EC patients (29 %) though this difference was not statistically significant.

The present myocardial infarction was transmural in 71 % of the EC patients and 63 % of the NEC patients, and non transmural in 29 % of the former group and 37 % of the latter Again, none of these differences was statistically significant.

Other cardiovascular disease

Other cardiovascular disease had previously been diagnosed in 29 AMI patients (13 %) of whom 17 were men (10 %) and 12 women (22 %) Intermittent claudication was the most common (17 patients) Other cardiovascular diseases involved were cerebrovascular disease (5) stenosis of the neck arteries (3) atrial septal defect (1) aortic valvular in sufficiency (1) operated ductus Botalli (1) and syndroma Raynaud (1) The distribution of these diseases was without any statistically significant difference between the EC (14 %) and NEC (18 %) patients.

Drug treatment

The AMI patients were questioned about their use of drugs, especially of beta-blockers and serum lipid lowering agents (clofibrate exclusively among AMI patients) Beta blockers were used by 59 patients (27 %) equally by both men and women, and clofibrate by 9 patients (4.1 %). No si[illegible] cant differences were found with respe[illegible] the use of these drugs between the EC ([illegible] and 4 %) and NEC (31 % and 4 %) pati[illegible]

Coronary risk factors in control subjects w[illegible] and without the ear lobe crease

In the control group there were 71 subje[illegible] (24 %) with EC and 219 subjects (76 [illegible] without it. The prevalence of this sign [illegible] thus the ratio of the EC subjects to the N[illegible] ones (distribution by age groups shown [illegible] Table 11) were low compared with A[illegible] patients. Otherwise, the following co[illegible] parisons are in agreement with the corr[illegible] sponding ones in the AMI group.

Blood pressure

History of arterial hypertension

Hypertension had been previously diagnose[illegible] more frequently in the NEC (20 %) than E[illegible] control subjects (15.5 %) but this was no[illegible] a statistically significant difference.

Systolic blood pressure

The mean systolic blood pressure was equal in the EC (141 ± 18.5 mmHg) and NEC subjects (140 ± 19 mmHg) without a statistically significant difference. Differences were also non significant when calculated by age groups (Fig 8)

Table 11 Control subjects classified as thos with (EC) or without (NEC) the ea lob crease by age. Figures in parentheses indicate percentages

Group	Age in years				
	30—39	40—49	50—59	60—65	Total
EC	1 (8)	21 (21)	44 (28)	5 (22)	71 (24)
NEC	12 (92)	78 (79)	111 (72)	18 (78)	219 (76)

F istributed equally among different activity groups (Fig. 11), so that there were no statistically significant differences here, either

Family history of premature cardiovascular disease and diabetes. Birthplace

Premature CHD was reported in the families of 30 of the EC and 33 of the NEC subjects. This small difference was not statistically significant.

Hypertension in the family was also more common in the EC (51) than in the NEC subjects (40 /) but the difference was statistically non-significant.

The family history for diabetes was positive in 29 of the EC and in 24 / of the NEC subjects. This difference was not also statistically significant.

The proportional distributions of the EC and NEC subjects and their parents according to birthplace (Fig 12) corresponded closely to those of the AMI group. The differences were small in all respects and statistically non-significant.

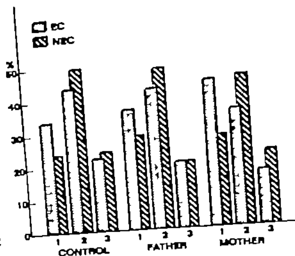


Fig. 12 Distribution of EC and NEC controls and their parents according to birthplace (1. west Finland, 2. east Finland, 3 Karelia).

Table 12 Distribution of EC and NEC controls by smoking habits. Figures in parentheses indicate percentages

Group	Current cigarette smoking < 20 per day	Current cigarette smoking ≥ 20 per day	Cigar/pipe	Ex-smokers	Non smokers	Total
EC	6 (8.5)	10 (14)	—	35 (49)	20 (28)	71
NEC	39 (18)	25 (11)	7 (3)	78 (36)	0 (32)	219

but more frequently ex-smokers (49 %) than the latter (36 %) Twenty cigarettes or more a day were smoked in both groups quite equally (Table 12) but smokers at lower levels were more frequent among NEC (18 %) than EC subjects (8.5 %) The differences were not statistically significant.

Diabetes mellitus

The prevalence of diabetes was 7 % in the EC and 4 % in the NEC subjects, which was a statistically non significant difference.

Obesity

The mean relative body weight was 0.261 ± 0 030 in the EC and 0.256 ± 0 033 in the NEC subjects. This difference was statistically non significant as were the differences in the age groups over 40 years (Fig 10)

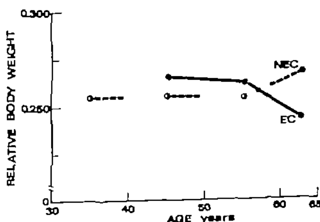


Fig 10 Mean relati e body weight of EC and NEC controls.

Level of physical activity

The greatest differences were in the inactive (I) and medium (II) physical activity groups at work (Fig 11) The NEC subjects were more inactive (43 %) whereas the EC subjects performed more light excercise (55 %) However the differences were not statistically significant.

With regard to the physical activity during leisure time the EC and NEC subjects were

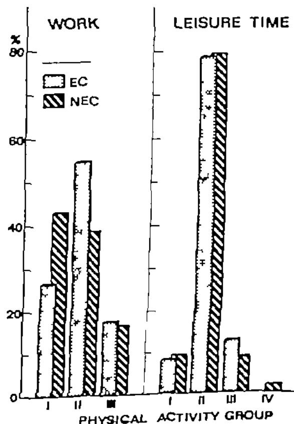


Fig 11 Distribution of EC and NEC controls according to level of the physical activity at work and during leisure time.

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Family history of premature cardiovascular disease and diabetes. Birthplace

Premature CHD was reported in the families of 30 of the EC and 33 of the NEC subjects. This small difference was not statistically significant.

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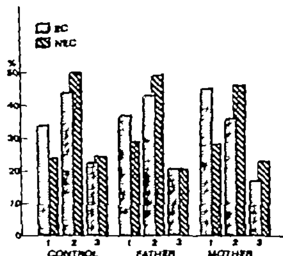


Fig. 12 Distribution of EC and NEC controls and their parents according to birthplace (1 west Finland, 2 east Finland, 3 Karelia).

B PATIENTS STUDIED BY CORONARY ANGIOGRAPHY

PREVALENCE OF THE DIAGONAL EAR LOBE CREASE

CHD patients

EC was present in 144 of 200 CHD patients (72 %) whereas it was absent in 56 patients (28 %) In this group there was only one patient under 30 years, and he had EC. Otherwise the presence of EC was rather infrequent in patients below 40 years In the age group 30 to 39 years it was seen in 10 of 27 patients (37 %) In the following decade EC was found in as many as 51 of 78 patients (65 %) and above 50 years the prevalence increased still further to 70 of 80 patients (87 %) aged 50 to 59 and 12 of 14 patients (86 %) aged 60 to 66 (Table 13) This increase with age was not, however statistically significant.

Below the age of 40 years EC was present more frequently unilaterally whereas above 40 years of age the bilateral EC became dominant, and this trend further increased with age

Table 13 Presence and absence of the ear-lobe crease in CHD patients by age Figures in parenthesis indicate percentages

Ear lobe crease	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Bilateral	—	3 (11)	35 (45)	53 (66)	10 (72)	101 (50.5)
Unilateral	1	7 (26)	16 (20)	17 (21)	2 (14)	43 (21.5)
Total	1	10 (37)	51 (65)	70 (87)	12 (86)	144 (72)
Absence	—	17 (63)	27 (35)	10 (12)	2 (14)	56 (28)

Table 14. Presence and absence of the ear lobe crease in non-CHD patients by age Figures in parentheses indicate percentages

Ear lobe crease	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Bilateral	—	1 (6)	4 (10)	5 (20)	2	12 (14)
Unilateral	—	—	4 (10)	2 (8)	—	6 (7)
Total	—	1 (6)	8 (20.5)	7 (28)	2	18 (21)
Absence	2	16 (94)	31 (79.5)	18 (72)	1	68 (79)

Non-CHD patients

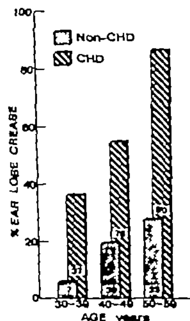
In the whole non-CHD group there were 68 of 86 patients (79 /o) without EC and 18 (21 o) with it. Neither of the two patients under 30 years had EC, and in the 30 to 39 age group only one of 17 patients (6 /) had it (Table 14). Over 40 years of age the prevalence increased so that at the ages of 40 to 49 years EC was present in 8 of 39 patients (20.5) and at the ages of 50 to 59 years in 7 of 25 patients (28 /), although the increasing prevalence with age was not statistically significant in this group either. Two of the 3 patients over 60 years had EC.

Comparison of the unilateral and bilateral EC was not feasible in this group because of their low prevalences.

CHD patients compared to non-CHD patients

EC was found in 72 / of the CHD group and in 21 of the non-CHD group, this difference being statistically highly significant ($p < 0.001$).

Most patients studied angiographically were between 30 and 59 years of ag During this period the prevalence of EC rose fo each decade in both groups, but the difference remained significant and even tended to increase with age (Fig 13). Taking into account all patients under 60 years of age EC was found in 71 / of the CHD group and in 19 / of the non-CHD group.



F g 13. Prevalence of the ear lobe crease in the largest ge groups of CHD and non-CHD patients. The numbers in the columns indicat the numbers of all individuals in each group.

Table 15. Presence (EC) and bsence (NEC) of th ea lobe crease in CHD patients by ge and extent of coronary atherosclerosis. Figures parentheses indicat percentages

Group	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
1-vessel disease						
EC	—	4 (29)	13 (59)	7 (64)	2	26 (52)
NEC	—	10 (71)	9 (41)	4 (36)	1	24 (48)
2-vessel disease						
EC	1	3 (43)	18 (69)	28 (93)	2	52 (79)
NEC	—	4 (57)	8 (31)	2 (7)	—	14 (21)
3-vessel disease						
EC	—	3 (50)	20 (67)	35 (90)	8 (89)	66 (79)
NEC	—	3 (50)	10 (33)	4 (10)	1 (11)	18 (21)

B PATIENTS STUDIED BY CORONARY ANGIOGRAPHY

PREVALENCE OF THE DIAGONAL EAR LOBE CREASE

CHD patients

EC was present in 144 of 200 CHD patients (72 %) whereas it was absent in 56 patients (28 %) In this group there was only one patient under 30 years, and he had EC Other wise the presence of EC was rather in frequent in patients below 40 years In the age group 30 to 39 years it was seen in 10 of 27 patients (37 %) In the following decade EC was found in as many as 51 of 78 patients (65 %) and above 50 years the prevalence increased still further to 70 of 80 patients (87 %) aged 50 to 59 and 12 of 14 patients (86 %) aged 60 to 66 (Table 13) This increase with age was not, however statisti cally significant.

Below the age of 40 years EC was present more frequently unilaterally whereas above 40 years of age the bilateral EC became dominant, and this trend further increased with age.

Table 13 Presence and absence of the ear lobe crease in CHD patients by age. Figures in parentheses indicate percentages

Ear lobe crease	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Bilateral	—	3 (11)	35 (45)	53 (66)	10 (72)	101 (50.5)
Unilateral	1	7 (26)	16 (20)	17 (21)	2 (14)	42 (21 5)
Total	1	10 (37)	51 (65)	70 (87)	12 (86)	144 (72)
Absence	—	17 (63)	27 (35)	10 (12)	2 (14)	56 (28)

Table 14 Presence and absence of the ear-lobe crease in non-CHD patients by age Figu es n paren theses indicate percentages

Ear lobe crease	Age in years					
	20—29	30—39	40—49	50—59	60—66	Total
Bilateral	—	1 (6)	4 (10)	5 (20)	2	12 (14)
Unilateral	—	—	4 (10)	2 (8)	—	6 (7)
Total	—	1 (6)	8 (20.5)	7 (28)	2	18 (21)
Absence	2	16 (94)	31 (79.5)	18 (72)	1	68 (79)

Systolic blood pressure

In the CHD group the mean systolic blood pressure was higher in all age groups than in the non-CHD group. For the whole groups the means were 137 ± 17 mmHg and 133 ± 18 mmHg, respectively ($p < 0.01$)

Diastolic blood pressure

The relation between the groups was similar for the diastolic blood pressure. The means were higher in the CHD than the non-CHD group. In the former group the mean was 88 ± 10 mmHg and in the latter 84 ± 9 mmHg. The difference was statistically significant ($p < 0.001$)

Serum lipids

Serum cholesterol

The mean serum cholesterol concentrations in the CHD and non-CHD groups are shown in Table 16. In different age groups the mean values were also significantly higher in the CHD group compared to the non-CHD group except between those aged 50 to 59 years.

Serum tr glyce des

The mean serum triglyceride concentrations were elev ted in all age groups of the CHD patients, but normal in all age groups of the non-CHD patients. The total means of the groups are presented in Table 16

Table 17 Distribution of CHD and non-CHD patients ccording to type of hyperlipoprote emia. Figures i parentheses indicate percentages

Group	No of pats	Type of hyperlipoproteinemia			
		0	II A	II B	IV
CHD	112	38 (34)	28 (33)	30 (27)	7 (6)
non-CHD	71	38 (53.5)	37 (39)	4 (6)	1 (1.4)

Serum total lipids

A similar ratio between the groups was apparent for serum total lipids as well (Table 16). The means rose with age in the same proportions in both CHD and non-CHD patients, so that similar differences were seen at each age group

Hyperlipoproteinemias

About a third of the CHD patients, but over a half of the non-CHD patients, had normal lipid values which excluded any type of hyperlipoproteinemia (Table 17). The differences between the groups were most obvious for type II B ($p < 0.001$) whereas for types II A and IV they were small (p NS).

Serum alpha lipop otein

The levels of serum alpha-lipoprotein were lower in all age groups of CHD patients compared to non-CHD patients, as also were the total group means (Table 16).

Table 16 Mea serum l pids CHD ad no -CHD patients. The differences between the groups were highly significant ($p < 0.001$)

Group	Cholesterol			Triglycerides			Total lipids			Alpha-lipoprotein		
	N	mmol/l	SD	N	mmol/l	SD	N	g/l	SD	N	g/l	S.D.
CHD	193	7.8	1.6	188	2.15	1.87	112	8.5	2.1	112	1.60	0.43
non-CHD	85	7.0	1.7	81	1.24	1.01	71	7.4	1.5	71	1.93	0.55

THE RELATIONSHIP OF THE EAR LOBE CREASE TO THE EXTENT OF CORONARY ATHEROSCLEROSIS

Single vessel disease

EC was seen in 26 of the 50 patients (52 %) with single vessel disease (Table 15) The prevalence was lowest at the ages of 30 to 39 in which group EC was found in only *4 of 14 patients (29 %)* but the *frequency* tended to increase with age (Fig 14) At the ages of 40 to 49 EC was found in 13 of 22 patients (59 %) and in the 50 to 59 age group in 7 of 11 (64 %) Two of the 3 patients over 60 years had EC.

Double vessel disease

The prevalence of EC also tended to increase with age in patients with double vessel disease (Fig 14) The prevalence was higher

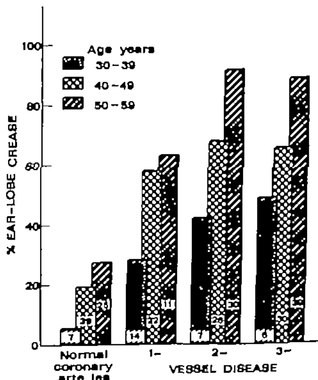


Fig 14 Prevalence of the ear lobe crease in patients studied by coronary angiography by age and extent of coronary atherosclerosis. The num bers in the columns indicate th numbers of all individuals in each group.

though not significantly in all age groups compared to those with single vessel disease EC was found in 52 of 66 patients (79 %) with double vessel disease. By age groups, it was present in 3 of 7 patients (43 %) at ages of *30 to 39 in 18 of 26 (69 %)* at 40 to 49 and in 28 of 30 (93 %) in the 50 to 59 age group Only one patient was below 30 years and 2 were over 60 all three had EC (Table 15)

Triple vessel disease

In triple vessel disease the prevalence of EC was fairly similar to that in double vessel disease. In the whole group 66 of 84 patients (79 %) had EC At the ages of 30 to 39 it was seen in 3 of 6 patients (50 %) at 40 to 49 years in 20 of 30 patients (67 %) and at 50 to 59 years in 35 of 39 patients (90 %) The group also included 9 patients over 60 years of whom 8 (89 %) had EC (Table 15 Fig 14) The prevalence of EC did not differ statisti cally significantly from that in single vessel disease

PREVALENCE OF CORONARY RISK FACTORS IN CHD AND NON CHD PATIENTS

The following risk factors are described for *the CHD and non-CHD groups, men and* women combined. In addition, the com parisons have been done between the men of both groups too but this is mentioned only if the two sets of results differed from each other

Blood pressure

History of arterial hypertension

Hypertension had been diagnosed before this study in 62 CHD patients (31 /) and in 15 patients of the non-CHD group (17) The difference was significant ($p < 0.01$)

Systolic blood pressure

In the CHD group the mean systolic blood pressure was higher in all age groups than in the non-CHD group. For the whole groups the means were 137 ± 17 mmHg and 133 ± 16 mmHg, respectively ($p < 0.01$)

Diastolic blood pressure

The relation between the groups was similar for the diastolic blood pressure. The means were higher in the CHD than the non-CHD group. In the former group the mean was 88 ± 10 mmHg and in the latter 84 ± 9 mmHg. The difference was statistically significant ($p < 0.001$)

Serum lipids

Serum cholesterol

The mean serum cholesterol concentrations in the CHD and non-CHD groups are *shown* in Table 16. In different age groups the mean values were also significantly higher in the CHD group compared to the non-CHD group except between those aged 50 to 59 years.

Serum triglycerides

The mean serum triglyceride concentrations were elevated in all age groups of the CHD patients, but normal in all ag groups of the non-CHD patients. The total means of the groups are presented in Table 16.

Table 17 Distribution of CHD and non-CHD patients according to type of hyperlipoproteinaemia. Figures in parentheses indicate percentages

Group	No. of pats.	Type of hyperlipoproteinemia			
		0	II A	II B	IV
CHD	112	38 (34)	28 (33)	30 (27)	7 (6)
non-CHD	71	38 (53 5)	37 (38)	4 (6)	1 (1.4)

Serum total lipids

A similar ratio between the groups was apparent for serum total lipids as well (Table 16) The means rose with age in the same proportions in both CHD and non-CHD patients, so that similar differences were seen at each age group.

Hyperlipoproteinemias

About a third of the CHD patients, but over a half of th non-CHD patients, had normal lipid values which excluded any type of hyperlipoproteinemia (Table 17) The differ ences between the groups were most obvious for type II B ($p < 0.001$) whereas for types II A and IV they were small (p NS).

S rum alpha lipoprotein

The levels of serum alpha-lipoprotein were lower in all age groups of CHD patients compared to non-CHD patients, as also were the total group means (Table 16)

Table 16 Mea serum lipids in CHD ad non CHD patients The differences between the groups were highly significant ($p < 0.001$)

Group	Cholesterol			Triglycerides			Total lipids			Alpha-lipoprotein		
	N	mmol.l	S D	N	mmol l	SD	N	g l	S.D.	N	g/l	S D.
CHD	103	7 8	1 6	108	2 15	1 37	112	8.5	2.1	112	1.50	0.43
non-CHD	83	7 0	1 7	81	1.4	1 01	71	7 4	1.5	71	1.93	0 55

THE RELATIONSHIP OF THE EAR LOBE CREASE TO THE EXTENT OF CORONARY ATHEROSCLEROSIS

Single vessel disease

EC was seen in 26 of the 50 patients (52 %) with *single vessel disease (Table 15)* The prevalence was lowest at the ages of 30 to 39 in which group EC was found in only 4 of 14 patients (29 %) but the frequency tended to increase with age (Fig 14) At the ages of 40 to 49 EC was found in 13 of 22 patients (59 %) and in the 50 to 59 age group in 7 of 11 (64 %) Two of the 3 patients over 60 years had EC

Double vessel disease

The prevalence of EC also tended to increase with age in patients with double vessel disease (Fig 14) The prevalence was higher

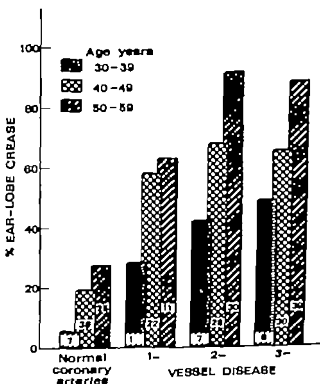


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In triple vessel disease the prevalence of EC was fairly similar to that in double vessel disease. In the whole group 66 of 84 patients (79 %) had EC. At the ages of 30 to 39 it was seen in 3 of 6 patients (50 %) at 40 to 49 years in 20 of 30 patients (67 %) and at 50 to 59 years in 35 of 39 patients (90 %) The group also included 9 patients over 60 years, of whom 8 (89 %) had EC (Table 15 Fig 14). The prevalence of EC did not differ statisti cally significantly from that in single vessel disease.

PREVALENCE OF CORONARY RISK *FACTORS IN CHD AND NON CHD* PATIENTS

The following risk factors are described for the CHD and non-CHD groups, men and women combined. In addition, the comparisons have been done between the men of both groups too but this is mentioned only if the two sets of results differed from each other

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History of arterial hypertension

Hypertension had been diagnosed before this study in 62 CHD patients (31) and in 15 patients of the non-CHD group (17 %) The difference was *significant* ($p < 0.01$)

Systolic blood pressure

In the CHD group the mean systolic blood pressure *was higher in all age groups than* in the non-CHD group. For the whole groups the means were 137 ± 17 mmHg and 133 ± 16 mmHg, respectively ($p < 0.01$).

Diastolic blood pressure

The relation between the groups was similar for the diastolic blood pressure. The means were higher in the CHD than the non-CHD group. *In the* former group the mean was 88 ± 10 mmHg and in the latter 84 ± 9 mmHg. The difference was statistically significant ($p < 0.001$).

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Serum cholesterol

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non-CHD	83	7.0	1 7	81	1 24	1 01	71	7 4	1 5	71	1.83	0 53

Smoking

In the CHD group there were 83 current smokers (41.5 %) 104 ex smokers (52 %) and 13 non smokers (6.5 %). This distribution differed considerably from that in the non-CHD group ($p < 0001$) in which non-smokers formed the largest classification with 42 patients (49 %) whereas smokers and ex smokers were distributed almost equally the former amounting to 20 (23 %) and the latter to 24 (28 %) The differences were smaller hovewer between the groups of non-CHD men and CHD men. Among the non-CHD men there were 11 current smokers (31 %) 17 ex smokers (49 %) and 7 non-smokers (20 %).

Diabetes mellitus

Diabetes, or a pathological glucose tolerance, was verified more frequently in the CHD than in the non-CHD group It was seen in 43 of the former group (21.5 %) and in only 8 (9 %) of the latter ($p < 0\ 05$)

Obesity

The mean relative body weight was 0.255 ± 0 031 in the CHD group and 0.245 ± 0 030 in the non CHD group The means also differed in a similar way ($p < 0\ 001$) in all age groups except for that over 60 years.

Blood group

The blood group was determined in 172 CHD patients and 65 non-CHD patients. There were 80 CHD patients (46 5 %) of blood group A, 30 (17 %) of B, 14 (8 %) of AB and 48 (28 %) of O The percentages for the non-CHD patients were very close (p NS) to these (41.5 %, 23 %, 7 7 %, and 27 7 %, respect ively)

Family history of premature cardio-vascular disease and diabetes. Birthp

Premature CHD in the family was r for 152 patients of the CHD group (hypertension for 73 fo them (36.5 diabetes for 47 (23.5 %).

In the non-CHD group by comparis prevalences of CHD and hypertension family differed for the whole group a the men only In the whole group 52 p (60.5 %) had CHD in the family th valence being somewhat lower for mer of 35 (46 %). Similarly the prevale hypertension in the family was high the whole group than for men only six patients in the whole group (53.5 13 men (37 %) had answered in the mative on this point. Diabetes existed families of 25 non-CHD patients (29

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THE DIAGONAL EAR LOBE CREASE CORONARY RISK FACTORS

The comparison covered the CHD and r CHD patients as separate groups. Both gro were likewise further divided into patie with the bilateral or unilateral EC (patients) and those without EC (N patients)

Coronary risk factors in CHD patients with and without the ear-lobe crease

The CHD group included 144 EC patients (72 %) and 56 NEC patients (28 %), as described more precisely earlier in this paper The statistical analysis was done between the total groups and also in different age groups.

Blood pressure

History of arterial hypertension

Hypertension had been previously diagnosed in 14 % of the EC and in 23 % of the NEC patients. The difference was not significant.

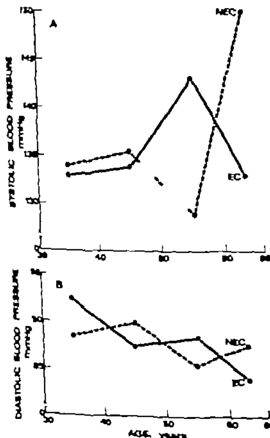


Fig 15 Mean systolic (A) and diastolic (B) blood pressure of EC and NEC patients in the CHD group

Systolic blood pressure

The mean systolic blood pressure was 138 ± 18 mmHg in the EC and 135 ± 15 mmHg in the *NEC* patients (p *NS*). The largest differences were between the 50 to 59 year age groups and those over 60 years, though in opposite directions (Fig 15).

Diastolic blood pressure

The mean diastolic blood pressure was almost equal in the EC and NEC groups, being 88 ± 11 mmHg in the former and 89 ± 9 mmHg in the latter The differences by age groups were also small and not significant (Fig 15).

Serum lipids

Serum cholesterol

The mean serum cholesterol values of the entire groups were similar at 7.8 ± 1.6 mmol/l in the EC and 7.7 ± 1.5 mmol/l in the NEC patients. By age groups the means varied to both sides of a hypothetical horizontal plane (Fig. 16), but again without statistical significance.

Serum triglycerides

Differences in mean serum triglycerides were statistically non-significant. In the EC patients the mean was 2.2 ± 1.8 mmol/l and in the NEC patients 2.1 ± 2.1 mmol/l. The values by age groups are presented in Fig. 16

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The mean serum total lipid value was the same, 8.5 g/l, in the EC (S.D ± 2.2) and in the NEC patients (S.D. ± 1.8), but in the two

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Diabetes, or a pathological glucose tolerance, was verified more frequently in the CHD than in the non-CHD group It was seen in 43 of the former group (21.5 %) and in only 8 (9 %) of the latter ($p < 0.05$)

Obesity

The mean relative body weight was 0.255 ± 0.031 in the CHD group and 0.245 ± 0.030 in the non-CHD group The means also differed in a similar way ($p < 0.001$) in all age groups except for that over 60 years.

Blood group

The blood group was determined in 172 CHD patients and 65 non-CHD patients. There were 80 CHD patients (46.5 %) of blood group A, 30 (17 %) of B 14 (8 %) of AB and 48 (28 %) of O The percentages for the non CHD patients were very close (p NS) to these (41.5 %, 23 %, 7.7 %, and 27.7 %, respectively)

Family history of premature cardiovascular disease and diabetes Birthplace

Premature CHD in the family was recorded for 152 patients of the CHD group (76 %) hypertension for 73 fo them (36.5 %) and diabetes for 47 (23.5 %)

In the non-CHD group, by comparison, the prevalences of CHD and hypertension in the family differed for the whole group and for the men only In the whole group 52 patients (60.5 %) had CHD in the family the prevalence being somewhat lower for men — 16 of 35 (46 %) Similarly the prevalence of hypertension in the family was higher for the whole group than for men only Forty six patients in the whole group (53.5 %) and 13 men (37 %) had answered in the affirmative on this point. Diabetes existed in the families of 25 non-CHD patients (29 %)

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THE DIAGONAL EAR LOBE CREASE AND CORONARY RISK FACTORS

The comparison covered the CHD and non CHD patients as separate groups. Both groups were likewise further divided into patients with the bilateral or unilateral EC (EC patients) and those without EC (NEC patients)

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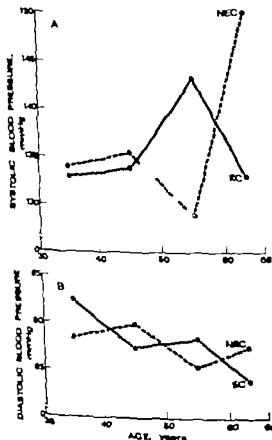


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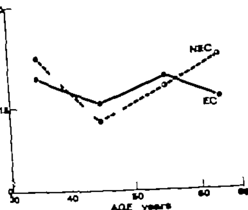
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g. 19 Mean serum alpha-lipoprotein of EC and EC patients in the CHD group.

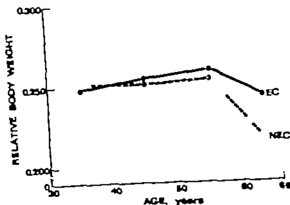


Fig 20 Mean relative body weight of EC and NEC patients in the CHD group.

9). The total means for the two groups were the same at 1.8 ± 0.4 g/l, so that a statistically significant difference was absent in this case, too.

Smoking

Among the EC patients there were 42 / current smokers, 52 ex smokers and 7 non-smokers, and these proportions were fairly similar for the NEC patients (41 /ₒ, 54 ₒ, and 5 /). The differences were not statistically significant

Diabetes mellitus

Diabetes, or t least a pathological glucose tolerance, was almost as frequent in the EC (21) as in the NEC patients (23), and again there was no statistically significant difference

Obesity

The mean relative body weight was 0.256 ± 0.032 in the EC and 0.251 ÷ 0.029 in the NEC patients This difference was not significant and neither were those f r all age groups (Fig. 20)

Blood group

The proportional differences between the EC and NEC groups were greatest for the blood groups A and O There were more EC (49 /) than NEC patients (40) of blood group A, whereas the prevalence was reversed for group O which included 25 ₒ of the EC and 36 of the NEC patients. The frequencies of blood groups B and AB differed little between the EC (18 / and 9 /) and NEC patients (17 and 6). All differences were statistically non-significant.

Family history of premature cardiovascular disease and diabetes. Birthplace

Differences in the family histories of the investigated diseases — CHD hypertension, and diabetes — did not reach statistical sig nificance in any respect. The relative propor tions were, for CHD 76 in the EC and 75 in the NEC patients, for hypertension 35 and 39 ₒ, and for diabetes 25 and 20 ₒ, respectively

Both the CHD patients and their parents in each group were distributed very similarly by birthplace. None of the regions showed statistically significant differences between the EC and NEC patients (Fig. 21).

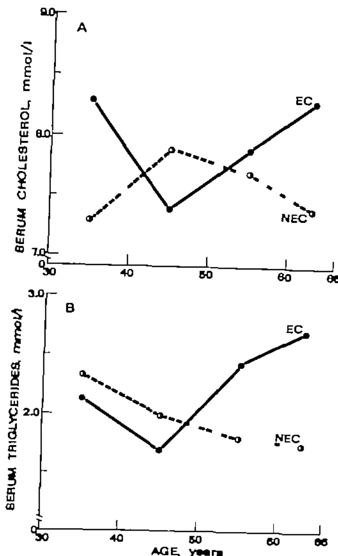


Fig. 16 Mean serum cholesterol (A) and triglycerides (B) of EC and NEC patients in the CHD group.

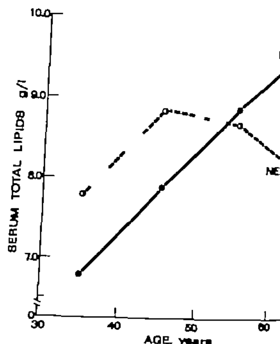


Fig 17 Mean serum total lipids of EC and patients in the CHD group.

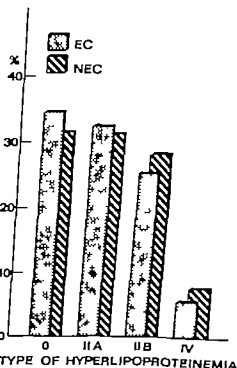


Fig 18 Distribution of EC and NEC patients th CHD group according to type of hyperlipo p teinemia.

youngest age groups the values were higher in the EC than NEC patients, and this situation was reversed in the two older groups (Fig 17) However these differences were not statistically significant.

Hyperlipoproteinemias

The proportional distribution of different classes of hyperlipoproteinemia (II A, II B and IV) was fairly uniform among both the EC and NEC patients (Fig 18), and failed to demonstrate any statistically significant differences.

Serum alpha lipoprotein

The EC and NEC patients resembled each other in the serum alpha lipoprotein range which was narrow in all age groups (Fig

THE HISTOPATHOLOGIC POSTMORTEM STUDY OF THE EAR LOBE

The postmortem study was an attempt to determine whether any definite histopathologic changes in the lobule portion of the auricle could be found to explain the formation of EC.

The ear lobes of 10 patients who had died from acute myocardial infarction were studied. The findings were compared to those of 10 age-matched control patients who died from a cause other than cardiovascular disease and were free of significant coronary atherosclerosis at autopsy. All patients with myocardial infarction had EC, whereas all control subjects were without EC. The age of both groups ranged from 43 to 65 years, with a mean of 56 years. There was only one woman in each group and both were 63 years old.

The samples from the lobules of the auricles were fixed in formalin. The sections were stained with hematoxylin-eosin, Weigert's elastic tissue stain, and Gomori's reticulum stain. The specimens were examined by two experienced pathologists, independently. The findings from the ear lobes included distended capillaries, some unspecific inflammatory changes around these and collagen degeneration being of the type caused by light. These features did not differ between the groups apart from the presence of more advanced acute stasis in patients with myocardial infarction. A single exception was a myocardial infarction patient aged 56 who also had significant sclerosis of the small arteries of the lobule of the auricle.

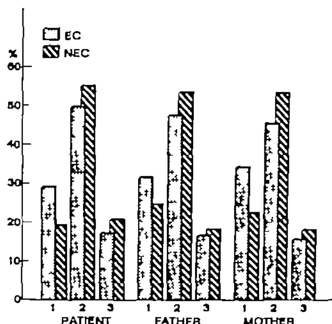


Fig 21 Distribution of EC and NEC patients and their parents in the CHD group according to birthplace (1. west Finland, 2. east Finland, 3. Karelia)

Other characteristics of CHD patients with and without the ear lobe crease

Previous and current history of CHD

Angina pectoris had been experienced for 5 8 ± 4.1 years by the EC patients and for 4 0 ± 3 0 years by the NEC patients. This difference was not statistically significant, and neither were those in all age groups. However symptomatic CHD had been present for longer in the EC than in the NEC patients.

There had been one or more myocardial infarction in 61 % of both EC and NEC patients, and no significant differences existed with respect to the numbers of previous infarctions, either

Coronary by pass operation had been performed in 35 % of the EC patients and in 30 % of the NEC patients (p NS)

Other cardiovascular disease

In the CHD group 33 patients (16.5 %) had some other cardiovascular disease, of which intermittent claudication was most general, involving 24 patients. Other diseases involved were stenosis of the neck arteries (5), atrial septal defect (2) and aortic stenosis (2). A previous history of a disease of this kind was recorded in 29 % of the EC and in 7 % of the NEC patients, again a difference which did not reach statistical significance.

Drug treatment

The use of beta blockers and serum lipid lowering agents (clofibrate being the most important) was relatively less common among the EC (64 % and 13 %) than among the NEC patients (75 % and 21 %). These small differences were not, however statistically significant.

Coronary risk factors in non-CHD patients with and without the ear lobe crease

The non-CHD group was small compared with the others, being made up of 86 patients, — 18 (21 %) with EC and 68 (79 %) without EC The statistical evaluation of the relationship between EC and coronary risk factors was only made between total EC and NEC patients, disregarding age and sex.

The differences in the distribution of risk factors between the EC and NEC patients were not statistically significant, with the exception of previous myocardial infarction. This had been diagnosed prior to the study in 6 of 86 non-CHD patients (7 %) of whom only one was without EC This interesting difference between the EC and NEC patients was statistically significant ($p < 0.01$).

THE HISTOPATHOLOGIC POSTMORTEM STUDY OF THE EAR LOBE

The postmortem study was an attempt to determine whether any definite histopathologic changes in the lobule portion of the auricle could be found to explain the formation of EC.

The ear lobes of 10 patients who had died from acute myocardial infarction were studied. The findings were compared to those of 10 age-matched control patients who died from a cause other than cardiovascular disease and were free of significant coronary atherosclerosis at autopsy. All patients with myocardial infarction had EC whereas all control subjects were without EC. The age of both groups ranged from 43 to 65 years, with a mean of 56 years. There was only one woman in each group and both were 65 years old.

The samples from the lobules of the auricles were fixed in formalin. The sections were stained with hematoxylin-eosin, Weigert's elastic tissue stain and Gomori's reticulum stain. The specimens were examined by two experienced pathologists, independently. The findings from the ear lobes included distended capillaries, some unspecific inflammatory changes around these and collagen degeneration being of the type caused by light. These features did not differ between the groups apart from the presence of more advanced acute stasis in patients with myocardial infarction. A single exception was a myocardial infarction patient aged 56 who also had significant sclerosis of the small arteries of the lobule of the auricle.

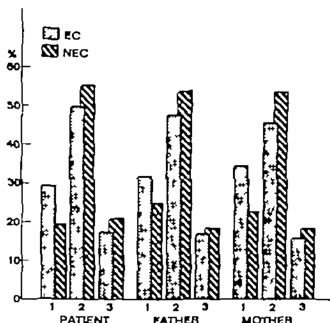


Fig 21 Distribution of EC and NEC patients and their parents in the CHD group according to birthplace (1 west Finland, 2. east Finland, 3. Karelia)

Other characteristics of CHD patients with and without the ear lobe crease

Previous and current history of CHD

Angina pectoris had been experienced for 5 8 ± 4.1 years by the EC patients and for 4 0 ± 3.0 years by the NEC patients. This difference was not statistically significant, and neither were those in all age groups However symptomatic CHD had been present for longer in the EC than in the NEC patients.

There had been one or more myocardial infarction in 61 % of both EC and NEC patients, and no significant differences existed with respect to the numbers of previous infarctions, either

Coronary by pass operation had been performed in 35 % of the EC patients and in 30 % of the NEC patients (p NS)

Other cardiovascular disease

In the CHD group 33 patients (16.5 %) had some other cardiovascular disease, of which intermittent claudication was most general, involving 24 patients. Other diseases involved were stenosis of the neck arteries (5), atrial septal defect (2) and aortic stenosis (2). A previous history of a disease of this kind was recorded in 29 % of the EC and in 7 % of the NEC patients, again a difference which did not reach statistical significance.

Drug treatment

The use of beta blockers and serum lipid lowering agents (clofibrate being the most important) was relatively less common among the EC (64 % and 13 %) than among the NEC patients (75 % and 21 %). These small differences were not, however statistically significant.

Coronary risk factors in non CHD patients with and without the ear lobe crease

The non-CHD group was small compared with the others, being made up of 86 patients, — 18 (21 %) with EC and 68 (79 %) without EC The statistical evaluation of the relationship between EC and coronary risk factors was only made between total EC and NEC patients, disregarding age and sex.

The differences in the distribution of risk factors between the EC and NEC patients were not statistically significant, with the exception of previous myocardial infarction. This had been diagnosed prior to the study in 6 of 86 non-CHD patients (7 /) of whom only one was without EC This interesting difference between the EC and NEC patients was statistically significant ($p < 0.01$)

Dear et al. 1971 Eliot et al. 1974). With these limitations in mind the control subject material of the present study should meet the requirements, being an age- and sex matched sample of the normal population, free of clinical coronary heart disease. Among the patients evaluated angiographically the group with normal coronary arteries was also small in the present study although larger than in any previous one.

In the present study the diagonal ear lobe crease was found to be present in a remarkably high proportion of patients with myocardial infarction, viz. 69 per cent of the total group and 66 per cent of those under 60 years of age, and there was a trend of correlation with the age of the patients. On the other hand, only 25 per cent of the age- and sex-matched control subjects had this sign. The prevalence of the ear lobe crease in this Finnish coronary heart disease material was thus high compared with previous similar studies (Lichstein et al. 1974, Christiansen et al. 1975), especially since these latter investigations included rather old patients, up to 69 years of age. This is noteworthy because it seems that the prevalence of the ear lobe crease increases as a function of age, which has led to the suggestion that it is associated merely with advanced age (Mehta and Hamby 1974). However in the present study the prevalence of the ear lobe crease was fairly high in all age groups of patients with acute myocardial infarction, even though it also tended to increase with age in these patients, too. The ear crease was already fairly common below 50 years of age, and the increase above 50 occurred smoothly without showing any sharp rise. Sex did not appear to cause differences in the prevalence of the ear crease of these patients at any age.

In the control subjects of the present study a similar increasing trend in the prevalence of the ear lobe crease in relation to age was observed in men, whereas in the women the sign was rather infrequent and detectable earliest at the age of 57 years. Both asymptomatic and symptomatic coronary atherosclerosis is well known to occur more frequently in young and middle-aged men and to progress more rapidly than in women of the same age (Blumgart et al. 1940 White et al. 1950 Zoll et al. 1951 Allison et al. 1963, Eggen and Solberg 1968 Strong et al. 1968, Tejada et al. 1968 Welch et al. 1970 and 1975). However in the present study the ear lobe crease was significantly less frequent in the age-matched sample of the normal population than in patients with acute myocardial infarction, and the effect of age did not seem to obscure the true positive association between the ear lobe crease and coronary heart disease.

Furthermore, these observations are strongly supported by the present findings in the patients with coronary heart disease documented by coronary angiography where the prevalence of the ear-lobe crease under 60 years of age (71 /) was similar to that in the patients with acute myocardial infarction. Also, the prevalence of the ear crease in the patients with normal coronary arteries or only insignificant coronary sclerosis (19 °) resembled that of the control subjects.

In addition to this, the diagonal ear lobe crease was more frequent in patients with more extensive coronary atherosclerosis. Lichstein et al. (1976) observed a similar trend while examining the association of the ear crease with the postmortem findings in coronary arteries. In their study the extent of coronary atherosclerosis in 59 patients with the bilateral ear crease was significantly more severe compared with the arteries of 32 patients with no ear crease. In the present study the ear crease was present in 52 per cent of the patients with single vessel disease and in 79 per cent of those with double or triple vessel disease. Even in those with only double vessel disease coronary angiography usually revealed ...

DISCUSSION

Since the discovery of the diagonal ear lobe crease, attempts have been made to clarify its significance and relationship to coronary heart disease. In the course of these investigations the ageing process has been found to have a prominent role of its own in this context.

Frank (1973) suggested that the ear lobe crease might be associated with premature cardiovascular disease. Lichstein et al. (1974) regarded it as a coronary risk factor as did Christiansen et al. (1975) on the basis of their study which resembled the former one. The ear crease was found to be infrequent under 50 years of age and thereafter to increase markedly especially in the latter study. The relationship of the ear crease to coronary heart disease, as confirmed by coronary angiography has been investigated by Sternlieb et al. (1974). They considered the relationship to be positive, whereas Mehta and Hamby (1974) suggested, on the basis of a similar material, that the ear lobe crease was correlated only with advancing age. The sign has also been noticed in connection with diabetic retinopathy and this has been presumed to indicate a correlation with generalized angiopathy (Andresen et al. 1976). Sprague (1976) considered the ear lobe crease to be a useful indicator of an operative risk and also to be related to coronary heart disease. Findings have thus been indicative of a positive relationship although the real nature of the diagonal ear lobe crease remains to be clarified and even its basic significance is still strongly suspected by some. The undoubted effect of age, in particular is the most important challenge to this possible relationship.

Forming a comparable patient and control material is obviously the main and most important difficulty in clinical research on coronary heart disease. The diagnosis of coronary heart disease, whether assessed by acute myocardial infarction or coronary angiography does not raise difficulties. The symptoms and signs of acute myocardial infarction are usually obvious and can be defined. Coronary angiography has also proved a reliable tool in the evaluation of coronary atherosclerosis, as shown by many comparative studies of postmortem findings (e.g. Kemp et al. 1967, Vlodaver et al. 1973, Grondin et al. 1974, Schwartz et al. 1975). The main difficulties arise in obtaining suitable control material. Subjects with no clinically demonstrable coronary heart disease are indeed easy to find, but some such individuals may have significant atherosclerotic changes in their coronary arteries (Enos et al. 1953, McNamara 1971). For ethical reasons coronary angiography cannot be done in a symptomless individual because of the risk involved. The proportion of subjects with angiographically normal coronary arteries is therefore bound to remain small. Some of these patients may in addition, suffer from another heart disease or ischemic heart disease without coronary atherosclerosis (e.g. Campeau et al. 1968,

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sclerosis, even though significant occlusive lesions were restricted to two main arteries.

Myocardial infarction had been previously diagnosed in 7 per cent of the patients with normal coronary arteries in the present study In the literature 1 1 to 16 per cent of all myocardial infarctions have been reported to occur in patients who do not demonstrate angiographic evidence of significant coronary atherosclerosis (e.g Campeau et al. 1968, Bruschke et al. 1971 Dear et al. 1971 Glancy et al. 1971 Kimbiris et al. 1972, Potts et al. 1972, Eliot et al. 1974, Thompson et al. 1977) The fact that 5 of the present 6 patients with past infarction and normal coronary arteries had the ear lobe crease deserves consideration. None of these patients had any other cardiovascular disease. Frank (1977) has also observed an association between the ear crease and ischemic heart disease without coronary atherosclerosis.

The presence of the ear lobe crease did not correlate with the duration of angina pectoris nor with the number of previous infarctions in the patients with acute myocardial infarction. Neither did the severity of the present myocardial infarction — either transmural or non transmural — influence the matter However angina pectoris showed a trend of longer duration in patients with angiographically documented coronary atherosclerosis and the ear lobe crease than in those without it, while the number of previous infarctions was fairly similar in both groups.

Apart from evaluating the relationship between the diagonal ear lobe crease and coronary heart disease the present study attempted to evaluate the relation of coronary risk factors to the ear lobe crease. On the basis of many prospective epidemiological studies (Keys 1970 Gertler and White 1976) coronary *risk factors may* definitely be said to increase the average risk of early coronary heart *disease in both sexes*, even though no strictly causal relationship has been established. The present study also indicated a greater prevalence of risk factors in patients with coronary heart disease than in controls, but none of the coronary risk factors was established as being related to the presence of the diagonal ear lobe crease when analyzed separately in patients with myocardial infarction, control subjects and patients studied by coronary angiography With regard to hypertension, diabetes and cigarette smoking Lichstein *et al.* (1974) have come to a conclusion of the same kind. Quite recently Rhoads *et al.* (1977) suggested that the ear lobe crease correlated with blood pressure and obesity but not with coronary heart disease.

None of the major coronary risk factors in the present study was associated with the ear lobe crease, — neither history of arterial hypertension, blood pressure values, cigarette smoking nor serum lipids. Serum lipids, especially elevated serum cholesterol, have been implicated in promoting the progression of coronary atherosclerosis (Bemis et al. 1973 Ben zvi et al. 1974), though not all observations favor this suggestion (Kimbiris et al. 1974, Frick et al. 1975 McLaughlin et al. 1977) In the present study the levels of serum lipids did not correlate with ear lobe crease though the patients with acute myocardial infarction of all age groups with the ear crease showed a trend towards higher means for serum cholesterol than those without it. The level of serum alpha lipoprotein was higher in the non-CHD than the CHD group, but not so in the patients without ear crease compared to those with it. Diabetes, the *level of physical activity at work and during* leisure time, obesity blood group and family *history of coronary* heart disease or diabetes were not associated with the ear crease either A history of hypertension in the families of the patients with myocardial infarction but without ear crease was obtained significantly more frequently than in those with the ear crease. However in the other groups no such relationship was seen. Rissanen (1974) has demonstrated that although

coronary heart disease is, in terms of both morbidity and mortality more prevalent in eastern than western Finland, there is no significant difference in the extent of coronary atherosclerosis between groups from these regions. The birthplace of the patients and subjects and their parents in the present study seemed *to have no effect on* the prevalence of the ear lobe crease, either

The possibility that the additive effect of the main risk factors known to have predictive value in individual subjects (Kannel et al. 1976) could still be related to the presence of the ear crease seems improbable, as the mean values of each risk factor in different age groups of the present study were rather similar This was further checked by calculating the risk score using the data of the Framingham study in the largest age groups of the present study No difference was observed between those with and without the ear crease. A discriminant function analysis of the risk factors in relation to the presence *of the ear lobe crease is in progress.*

The possibility of the ear lobe crease being associated with the drug treatment of coronary heart disease was not supported by the present results. Beta-blockers, especially practolol, have been reported to cause side effects in the skin. These include a lupus erythematosus-like syndrome (Raftery and *Denman 1973) and eczema, exfoliative dermatitis*, lichen planus, and a psoriasis-like rash (Felix t al. 1974). The present study did not suggest the ear-lobe crease to be a possible side effect of beta-blockers or other drugs.

The present results allow some speculation about the formation of the ear lobe crease and ts relation to the age of the individual and the extent of coronary heart disease. It seems probable that the ear-lobe crease often starts unilaterally and later develops bilaterally and earlier in men than in women. The unilateral ear crease is fairly frequent compared with the bilateral sign in men under 50 years of age and in women up to 60 years, after which the bilateral sign becomes dominant. On the other hand, the prevalence of the ear crease seems related to the severity and extent of coronary atherosclerosis, which in turn also usually correlates with the age of the patients, though with frequent exceptions. This might favor the view that both the ear crease and coronary heart disease share biological age as their common dominator

In the present study the youngest patient with coronary heart disease was 26 years old, and he had the ear crease. Sprague (1976) has found this sign in still younger patients, aged 3, 14, and 17 years. There is some evidence that pathological changes leading to coronary heart *disease might be initiated* very early in childhood. In studies on the coronary arteries of infants and children of parents with a high hereditary risk of coronary heart disease, intimal and musculo-elastic layer thickenings in coronary arteries have been reported (Neufeld et al. 1962, Vlodaver et al. 1969 Pesonen 1974). These *presumably genetically transmitted changes* may predispose to premature coronary atherosclerosis.

The development of coronary arteries precedes that of the ear lobula. Therefore, simultaneous embryological mis-development cannot be proposed as a basis for a later association of the ear-lobe crease with coronary heart disease. A common genetic factor responsible for both the ear crease and coronary atherosclerosis could be speculated upon, though. Certain anthropological facts deserve ttention in this respect. Halonen (1938) has found Finns to differ considerably from Japanese in the form of branching of coronary arteries and in the vascularization areas *of these in the myocardium.* The present study indicates that the prevalence of the ear lobe crease also differs considerably between Finns and Japanese with coronary heart disease. In the 50 to 59 year age group it appeared in 71 per cent of Finnish men, but in only 23.1 per cent of Japanese men (Rhoads et al. 1977), the latter figure corresponding

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closest to the prevalence of the ear lobe crease in the control subjects of the present material. The same genetic factor to determine branching and vascularization areas of coronary arteries might also determine the susceptibility to coronary heart disease and the ear lobe crease.

The lobule of the auricle is covered by skin. The subcutaneous tissue is abundant and encloses numerous fat cells. The rich capil lary bed and the relative paucity of nerve endings are characteristic features. The histopathologic changes in the investigated speci mens were slight. Distended capillaries were more frequently found in the patients with myocardial infarction, but this reflects only the existence of a more general stasis in these patients. The significant atherosclerosis found in one specimen cannot be cause of the ear-lobe crease because the others were without similar changes. Adams et al. (1974) have noticed a correlation between coronary atherosclerosis and changes in the Achilles' tendon, and considered the cause to be ageing avascular connective tissue. Some other studies indicate that collagen tissue might play a part in the pathogenesis of atherosclerosis (Cardinale and Udenfriend 1974 Ooshima et al. 1975 and 1977 Fuller et al. 1976 Prockop et al. 1976) However the light microscope was not sufficiently sensitive to reveal any significant collagen tissue changes in specimens of the present examination.

Conclusion

The prevalence of the diagonal ear lobe crease is considerably higher in patients with acute myocardial infarction or coronary heart disease documented angiographically compared to control subjects with no clinically detectable coronary heart disease or to those with normal coronary arteries. In addition, the ear lobe crease is more frequent in the more severe cases of coronary atherosclerosis. In all groups the prevalence of the ear crease tends to increase with age. Coronary risk factors seem not to be associated with this sign. In a few patients the ear lobe crease was present in ischemic heart disease with normal coronary arteries. More studies are needed to clarify the precise value of the ear lobe crease as a clinical sign associated with coronary heart disease. A prospective study would be particularly useful in this respect.

SUMMARY

The purpose of the present study was to investigate the relationship of the diagonal ear lobe crease to coronary heart disease and coronary risk factors and, in addition, to evaluate the development of the ear lobe crease.

The clinical material consisted of 219 patients with acute myocardial infarction fulfilling the WHO criteria, 290 control subjects, and 284 patients studied by coronary angiography. The latter group comprised 200 CHD and 86 non-CHD patients. In each group, except for the non-CHD patients, women were in a minority. The age of the investigated patients and subjects ranged from 26 to 66 years, the majority being under 60.

Below 60 years of age the prevalence of the ear lobe crease was 66 % in the patients with myocardial infarction and 25 % in the control subjects — the corresponding values being 71 % in the CHD and 19 % in the non-CHD patients. The prevalence increased with advancing age in all groups without affecting the positive association between the ear-lobe crease and coronary heart disease. The bilateral sign became more dominat than the unilateral one with age, too.

The prevalence of the ear lobe crease also increased with the extent of coronary atherosclerosis. The ear crease was seen in 52 % of the patients with single vessel disease and 79 % of the patients with double or triple vessel disease. In the non-CHD patients the sign was found in 21 % of the total group. Five of 6 non-CHD patients with previously diagnosed myocardial infarction and normal coronary arteries had the ear crease.

The ear-lobe crease was not correlated with the duration of symptomatic coronary heart disease, and neither were any of the investigated established coronary risk factors positively related to the sign. These included heredity, the major risk factors — hypertension, hyperlipidemia, and cigarette smoking — and certain minor factors: diabetes, level of physical activity, obesity etc. The presence of other cardiovascular disease did not influence this sign either.

The postmortem study of ear-lobe samples from 10 patients with ear crease and acute myocardial infarction and from 10 controls without ear crease or signs of any cardiovascular disease revealed non-specific histopathologic changes in both groups.

closest to the prevalence of the ear lobe crease in the control subjects of the present material. The same genetic factor to determine branching and vascularization areas of coronary arteries might also determine the susceptibility to coronary heart disease and the ear lobe crease.

The lobule of the auricle is covered by skin. The subcutaneous tissue is abundant and encloses numerous fat cells. The rich capillary bed and the relative paucity of nerve endings are characteristic features. The histopathologic changes in the investigated specimens were slight. Distended capillaries were more frequently found in the patients with myocardial infarction, but this reflects only the existence of a more general stasis in these patients. The significant atherosclerosis found in one specimen cannot be cause of the ear lobe crease because the others were without similar changes. Adams et al. (1974) have noticed a correlation between coronary atherosclerosis and changes in the Achilles' tendon, and considered the cause to be ageing avascular connective tissue. Some other studies indicate that collagen tissue might play a part in the pathogenesis of atherosclerosis (Cardinale and Udenfriend 1974, Ooshima et al. 1975 and 1977, Fuller et al. 1976, Prockop et al. 1976). However the light microscope was not sufficiently sensitive to reveal any significant collagen tissue changes in specimens of the present examination.

Conclusion

The prevalence of the diagonal ear lobe crease is considerably higher in patients with acute myocardial infarction or coronary heart disease documented angiographically compared to control subjects with no clinically detectable coronary heart disease or to those with normal coronary arteries. In addition, the ear lobe crease is more frequent in the more severe cases of coronary atherosclerosis. In all groups the prevalence of the ear crease tends to increase with age. Coronary risk factors seem not to be associated with this sign. In a few patients the ear lobe crease was present in ischemic heart disease with normal coronary arteries. More studies are needed to clarify the precise value of the ear lobe crease as a clinical sign associated with coronary heart disease. A prospective study would be particularly useful in this respect.

21. Doering, C., Ruhsenberger, C. & Philips, D. R. Ear lobe crease in heart disease. J Am Geriatr Soc 25: 183, 1977.

22. Dolder, M. A. & Oliver, M. F. Myocardial infarction in young men. Study of risk factors in nine countries. Br Heart J 37: 493, 1975.

23. Eggen, D. A. & Solberg, L. A. Variation of atherosclerosis with age. Lab Invest 18: 571, 1968.

24. Eliot, R. S., Baroldi, G. & Leone, A. Necropsy studies in myocardial infarction with minimal or no coronary luminal reduction due to atherosclerosis. Circulation 44: 1127, 1974.

25. Enos, W. F., Holmes, R. H. & Beyer, J. Coronary disease among United States soldiers killed in action in Korea. JAMA 152: 1090, 1953.

26. Epstein, F. H. & Ostrander, L. D. J. Detection of individual susceptibility toward coronary disease. Progr Cardiovasc Dis 13: 324, 1971.

27. Fejfar, Z. Prevention of ischaemic heart disease in the light of mortality and morbidity data. In: Early phases of coronary heart disease. Skandia International Symposia (ed. J. Waldenström, T. Larsson and N. Ljungstedt) Nordiska Bokhandelns Förlag, Stockholm 1973.

28. Felix, R. H., Ive, F. A. & Dahl, M. G. C. Cutaneous and ocular reactions to practolol. Br Med J 4: 321, 1974.

29. Frank, S. T. Aural sign of coronary-artery disease. N Engl J Med 289: 327, 1973.

30. Frank, S. T. Ear-crease sign of coronary disease. N Engl J Med 297: 282, 1977.

31. Frick, M. H., Valle, M., Harjola, P. T. & Korhola, O. Changes in native coronary arteries after coronary by-pass surgery. Role of graft patency, serum lipids and hypertension. Am J Cardiol 36: 744, 1975.

32. Friedberg, C. K. Some comments and reflections on changing interests and new developments in angina pectoris. Circulation 46: 1037, 1972.

33. Friedberg, C. K. The early diagnosis of coronary heart disease. Critical review. Adv Cardiol 8 (ed. P. I. Halonen and A. Louhija) Karger, Basel 1973.

34. Fuller, G. C., Matoney, A. L., Fisher, D. O., Fausto, N. & Cardinale, G. J. Increased collagen synthesis and the kinetic characteristics of prolyl hydroxylase in tissues of rabbits with experimental arteriosclerosis. Atherosclerosis 24: 483, 1976.

35. Gertler, M. M. & White, P. D. Coronary heart disease. A 25-year study in retrospect. Medical Economics Company, New Jersey 1976.

36. Glancy, D. L., Marcus, M. L. & Epstein, S. E. Myocardial infarction in young women with normal coronary arteriograms. Circulation 44: 495, 1971.

37. Grondin, C. M., Dyrda, I., Pasternac, A., Campeau, L., Bourassa, M. G. & Lesperance, J. Discrepancies between cinearteriographic and post-mortem findings in patients with coronary artery disease and recent myocardial revascularization. Circulation 49: 703, 1974.

38. Halonen, P. I. Die Koronararterien des menschlichen Herzens. Mit besonderer Berücksichtigung der Anastomosenfrage. Acta Soc Med Duodecim ser A, 21: 1, 1938.

39. Hood, W. B. Pathophysiology of ischemic heart disease. Progr Cardiovasc Dis 14: 297, 1971.

40. Kajanoja, P. A study in the morphology of the Finns and its relation to the settlement of Finland. Ann Acad Sci Fenn. Ser A V Med 146, 1971.

41. Kannel, W. B., McGee, D. & Gordon, T. A general cardiovascular risk profile: The Framingham study. Am J Cardiol 38: 46, 1976.

42. Kemp, H. G., Evans, H., Elliott, W. C. & Gorlin, R. Diagnostic accuracy of selective coronary cinearteriography. Circulation 36: 526, 1967.

43. Keys, A. Coronary heart disease in seven countries. Circulation (Suppl) 41: 1, 1970.

44. Keys, A., Aravanis, C., Blackburn, H., Buchem, F. S. P. van, Buzina, R., Djordjevic, B. S., Fidanza, F., Karvonen, M. J., Menotti, A., Puddu, V. & Taylor, H. Probability of middle-aged men developing coronary heart disease in five years. Circulation 45: 815, 1972.

45. Khosla, T. & Lowe, C. R. Indices of obesity derived from body weight and height. Br J Prev Soc Med 21: 122, 1967.

46. Kimbiris, D., Lavine, P., Broek, H. van den, Najmi, M. & Likoff, W. Devolutionary pattern of coronary atherosclerosis in patients with angina pectoris. Am J Cardiol 33: 7, 1974.

47. Kimbiris, D., Segal, B. L., Munir, M., Katz, M. & Likoff, W. Myocardial infarction in patients with normal patent coronary arteries as visualized by cinearteriography. Am J Cardiol 29: 724, 1972.

48. Lewis, B., Wootton, I. D. P., Krikler, D. M., February, A., Chait, A., Oakley, C. M., Sigurdsson, G. & Maurer, B. Frequency of risk

REFERENCES

1 Adams, C. W M., Bayliss, O B Baker R. W R., Abdulla Y H. & Hunter-Craig, C. J Lipid deposits in ageing human arteries, ten dons and fascia. Atherosclerosis 19 429 1974.

2. Allison, S P Chamberlain M. J & Hinton, P Intravenous glucose tolerance, insulin, glucose and free fatty acid levels after myocardial infarction. Br Med J 4 776, 1969

3 Allison, R. B., Rodriguez, F L., Higgins, E. A. Jr Leddy J P Abelmann, W H., Ellis, L. B. & Robbins, S L. Clinicopathologic correlations in coronary atherosclerosis. Four hundred thirty patients studied with post mortem coronary angiography Circulation 27 *170 1963*

4. Andresen, A. R., Christiansen J S & Jensen, J K. Diagonal ear lobe crease and diabetic retinal angiopathy N Engl J Med 294 1182, 1976

5 Andresen, A. R Mathiesen, B Calberg, H. & Christiansen, J S. Forekomsten af øreflipfure ved iskaemisk hjertesygdom. Ugeskr Laeger 137 2771 1975

6. Ask Upmark, E. Bedside medicine. 2nd ed. Almqvist & Wiksell, Stockholm 1969

7 Beaumont, J L., Carlson, L. A., Cooper G R., Fejfar Z., Fredrickson, D S & Strasser T *Classification of hyperlipidaemias* and hyperlipoproteinemias. Bull WHO 43 891, 1970.

8. Bemis, C. E., Gorlin, R., Kemp, H G & Herman M. V Progression of coronary artery disease. A clinical arteriographic study Circulation 47 455, 1973.

9 Ben zvi, J Hildner F J Javier R. P Fester A & Samet, P Progression of coronary artery disease. Cinearteriographic and *clinical observations in* medically and surgically treated patients. Am J Cardiol 34 295 1974.

10. Berg K., Boerresen, A. L. & Dahlén, G Serum high-density lipoprotein and atherosclerotic *heart-disease. Lancet 1 499 1974.*

11. Biörck, G Blomqvist, G & Sievers, J Cholesterol values in patients with myocardial infarction and in a normal control group. Acta Med Scand 493, 1957

12. Blackburn, H. Progress in the epidemiology and prevention of coronary heart disease. Progr Cardiol 3 (ed. P N Yu and J F Goodwin) Lea & Febiger Philadelphia 1974.

13. Blumgart, H. L., Schlesinger M. J & Davis, D Studies on the relation of clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings With particular reference to significance of collateral circulation. Am Heart J 19 1 1940.

14. Bruschke, A. V G Bruyneel, K. J J Bloch, A. & Herpen, G van Acute myocardial infarction without obstructive coronary artery disease demonstrated by selective cinearteriography Br Heart J *33 545, 1971*

15 Campeau, L., Lespérance, J Bourassa, M. G. & Ashekian, P B. Myocardial infarction without obstructive disease at coronary arteriography Can Med Assoc J 99 837 1968.

16. Cardinale, G J & Udenfriend, S Prolyl hydroxylase. Advanc Enzymol 41 245, 1974.

17 Christiansen, J S Mathiesen, B., Andresen, A. R & Calberg, H Diagonal ear lobe crease in coronary heart disease. N Engl J Med 293 308, 1975.

18 Day L. J Thibault, G E. & Sowton, E. Acut coronary insufficiency Review of 46 patients. Br Heart J 39 363, 1977

19 Dear H. D., Russell, R. O Jones, W B. & Reeves, T J Myocardial infarction in the bsence of coronary occlusion. Am J Cardiol 28 718, 1971

20 Dodds, C. & Mills, G L. Influence of myocardial *infarction on plasma-lipoprotein* concentration. Lancet 1 1160, 1959

77 Sternlab, J J Gau, G. T Davis, G D Rutherford, B. D. & Frye, R. L. The ear crease sign in coronary artery disease (Abstract). Circulation (Suppl) 3 III—132, 1974.

78. Strong, J P Solberg, L. A. & Restrepo, C. Atherosclerosis in persons with coronary heart disease. Lab Invest 18 527 1968.

79 Tejada, C., Strong, J P Montenegro, M. R., Restrepo, C. & Solberg, L. A. Distribution of coronary and aortic atherosclerosis by geographic location, race and sex. Lab Invest 18 509, 1968

80 Thompson, S. L, Vieweg, W V R., Alpert, J. S & Hagan, A. D Incidence and age distribution of patients with myocardial infarction and normal coronary arteriograms. Cath Cardiovasc Diag 3 1 1977

81. Welch, C. C., Proudfit, W L. & Sheldon, W C. Coronary arteriographic findings in 1000 women under age 50. Am J Cardiol 25 231, 1975.

82. Welch, C. C., Proudfit, W L., Sones, F M Shirey E. K Sheldon, W C. & Razavi, M. Cinecoronary arteriography in young men Circulation 42 647 1970

83 Welin, G Om serumkolesterinet vid hjartinfarkt. Nord Med 37 324, 1948

84. Werko, L Risk factors and coronary heart disease — facts or fancy? Am Heart J 91 87 1976

85 White, N K., Edwards, J E. & Dry T J.. The relationship f the degree f coronary therosclerosis with age, in men. Circulation 1 645, 1950.

86 Wilhelmsen, L., Tibblin, G., Fodor J & Werko, L. A multifactorial primary preventive trial in Gothenburg, Sweden. In Coronary heart disease and physical fitness (ed. O. A. Larsen and R. O Malmborg). Munksgaard, Copenhagen 1971

87 Vlodaver Z. & Edwards, J E. Pathology of coronary therosclerosis. Progr Cardiovasc Dis 14 256, 1971

88. Vlodaver Z., French, R Tassel, R. A. van & Edwards, J E. Correlation of the antemortem coronary arteriogram and the postmortem specimen. Circulation 47 162, 1973.

89 Vlodaver Z., Kahn, H A. & Neufeld, H. N The coronary arteries in early life in three different ethnic groups. Circulation 39 541, 1969.

90 Working Group of Ischaemic Heart Disease Registers 1971, Copenhagen. Report of the 5th working group with second revision f the operating protocol Regional Office for Europe, World Health Organization EURO 8010(3), Copenhagen 1971

91 Zoll, P M., Wessler S & Blumgart, H. L. Angina pectoris a clinical and pathologic correl tion Am J Med 11 331, 1951

factors for ischaemic heart-disease in a healthy British population. With particular reference to serum-lipoprotein levels. Lancet I 141 1974.

49 Lichstein, E., Chadda K. D Naik, D. & Gupta, P K. Diagonal ear lobe crease incidence and significance as a coronary risk factor (Abstract) Clin Res 21 949 1973.

50. Lichstein, E., Chadda, K. D Naik, D & Gupta P K. Diagonal ear lobe crease prevalence and implications as a coronary risk factor N Engl J Med 290 615 1974.

51 Lichstein, E., Chapman, L., Gupta, P K., Chadda, K. D Smith, H., Schwartz, I. & Naik, D Diagonal ear lobe crease and coronary artery sclerosis. Ann Intern Med 85 337 1976.

52. McLaughlin, P R., Berman N D Morton, B C., Schwartz, L. & Morch, J E. Long term angiographic assessment of the influence of coronary risk factors on native coronary circulation and saphenous vein aortocoronary grafts. Am Heart J 93 327 1977

53 McNamara J J Molot, M. A., Stremple, J F & Cutting, R. T Coronary artery disease in combat casualties in Vietnam. JAMA 216 1185 1971.

54. Mehta, J & Hamby R. L Diagonal ear lobe crease as a coronary risk factor N Engl J Med 291 260 1974.

55 Miettinen, M. Serial studies of serum lipids and lipoproteins in acute myocardial infarction. Ann Med Intern Fenn 46 69 1957

56 Miller G J & Miller N E. Plasma high density lipoprotein concentrations and development of ischaemic heart disease. Lancet 1 16 1975

57 Neufeld, H. N Wagenwoort, C A. & Edwards, J E. Coronary arteries in fetuses, infants, juveniles and young adults. Lab Invest 11 837 1962.

58 Nicolaysen R. & Westlund, K. Plasma lipids in coronary heart disease. Scand J Clin Lab Invest 15 291 1963

59 Nikkilä, E. Studies on the lipid protein relationship in normal and pathologic sera and the effect of heparin on serum lipoproteins Scand J Clin Lab Invest (Suppl) 5 8 1953.

60 Ooshima, A., Fuller G. C Cardinale G J Spector S & Udenfriend, S. Collagen biosynthesis in blood vessels of brain and other tissues of th hypertensive rat. Science 190 898 1975.

61 Ooshima, A., Fuller G C., Cardinale, G J Spector S & Udenfriend, S. Reduction of collagen biosynthesis in blood vessels and other tissues by reserpine and hypophysectomy Proc Nat Acad Sci (Wash.) 74 777 1977

62. Pesonen, E. Coronary wall thickening in children. Atherosclerosis 20 173, 1974.

63. Potts, K. H., Stein, P D & Houk, P C. Transmural myocardial infarction with arteriographically normal appearing coronary arteries. Chest 62 549 1972.

64. Prockop, D J Berg, R. A., Kivirikko, K. I & Uitto J Intracellular steps in the biosynthesis of collagen. In Biochemistry of collagen (ed. G N Ramachandran and A. H. Reddi) Plenum Press, New York 1976.

65. Proudfit, W L., Shirey E. K. & Sones, F M. Selective cine coronary arteriography correlation with clinical findings in 1000 patients. Circulation 33 901 1966.

66 Raftery E. B. & Denman A. M. Systemic lupus erythematosus syndrome induced by practolol. Br Med J 2 452, 1973.

67 Rhoads, G G Klein, K., Yano, K. & Preston, H. The earlobe crease — sign of obesity in middle-aged Japanese men. Hawaii Med J 36 74, 197

68. Rhoads, G G & Yano K. Ear lobe crease and coronary artery heart disease. Ann Intern Med 87 245, 1977

69 Rissanen, V Coronary and aortic atherosclerosis in Finnish men born in various regions of the country Atherosclerosis *0 495 1974.

70. Romo M. Factors related to sudden death in acute ischaemic heart disease. Acta Med Scand (Suppl) 547 1972.

71 Rose, G A. & Blackburn, H. Cardiovascular survey methods. WHO Monogr Ser 56, 1968.

72. Saltin, B. & Grimby G Physiological analysis of middle-aged and old former athletes Circulation 38 1104, 1968.

73. Schwartz, J N Kong, Y Hackel, D B. & Bertel A. G Comparison of angiographic and postmortem findings in patients with coronary artery disease. Am J Cardiol 36 174, 1975

74 Sowton E. Cardiac infarction and glucose-tolerance test. Br Med J 1 84 1962.

75 Sprague, D. H. Diagonal ear lobe crease as an indicator of operati e risk. Anesthesiology 45 362, 19 6.

76. Stamler J Berkson, D M & Lindberg, H. A. Risk factors Their rol in the etiology and pathogenesis of the atherosel rotic diseases. In Pathogenesis f atherosclerosis (ed. R. W Wissler and J C. Geer). Williams & Wilkins, Baltimore 1972.

77. Sternlieb, J J Gau, G. T Davis, G D., Rutherford, B. D. & Frye, R. L. The ear crease sign in coronary artery disease (Abstract). Circulation (Suppl) 3 III—152, 1974.

78. Strong, J P Solberg, L. A. & Restrepo, C. Atherosclerosis in persons with coronary heart disease. Lab Invest 18 527 1968.

79. Tejada, C., Strong, J P Montenegro, M. R., Restrepo, C. & Solberg, L. A. Distribution of coronary and aortic atherosclerosis by geographic location, race and sex. Lab Invest 18 509, 1968.

80. Thompson, S. L, Vieweg, W V R., Alpert, J S. & Hagan, A. D Incidence and age distribution of patients with myocardial infarction and normal coronary arteriograms. Cath Cardiovasc Diag 3 1, 1977

81. Welch, C. C Proudfit, W L. & Sheldon, W C Coronary arteriographic findings in 1000 women under age 50. Am J Cardiol 35 211 1975.

82. Welch, C C., Proudfit, W L., Sones, F M., Shirey E K Sheldon, W C & Razavi, M. Cinecoronary arteriography in young men. Circulation 42 647 1970.

83. Welin, G Om serumkolesterinet vid hjart infarkt. Nord Med 37 324, 1948

84. Werko, L. Risk factors and coronary heart disease — facts or fancy? Am Heart J 91 87 1976

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86. Wilhelmsen, L., Tibblin, G., Fodor J & Werko, L. A multifactorial primary preventive trial in Gothenburg, Sweden. In. Coronary heart disease nd physical fitness (ed. O A. Larsen and R. O. Malmborg). Munksgaard, Copenhagen 1971.

87. Vlodaver Z. & Edwards, J E. Pathology of coronary therosclerosis. Progr Cardiovasc Dis 14 256, 1971

88. Vlodaver Z., French, K., Tamel, R. A. van & Edwards, J E. Correlation of the antemortem coronary arteriogram and the postmortem specimen. Circulation 47 162, 1973.

89. Vlodaver Z Kahn, H. A. & Neufeld, H. N.. The coronary arteries in early life in three different ethnic groups. Circulation 39 541, 1969

90. Working Group of Ischaemic Heart Disease Registers. 1971, Copenhagen. Report f the 5th working group with second revision of the operating protocol. Regional Office for Europe, World Health Organization. EURO 8010(5), Copenhagen 1971.

91. Zoll, P M., Wessler S. & Blumgart, H. L. Angina pectoris clinical and pathologic correlation. Am J Med 11 331, 1951.

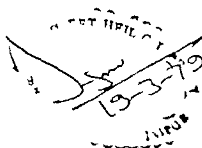
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Supplementum 620

3901

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By Ilkka Torstila



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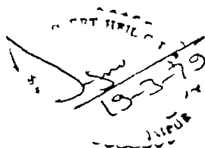
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29	22:	guinea pig	guinea pig ileum

FROM THE WIHURI RESEARCH INSTITUTE, HELSINKI,
AND FROM THE FIRST DEPARTMENT OF MEDICINE,
UNIVERSITY OF HELSINKI, FINLAND

The Plasma Kinin System in Acute Myocardial Infarction

BY
ILKKA TORSTILA

CONTENTS

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So far however the importance of the role of the plasma kinin system in this disease emains obscure This is mainly due to difficulties in the methodology of kinin research as well as to difficulties in the interpretation of the observed changes in the kinin system in relation to the pathophysiological events

The investigation presented here was designed to study the plasma k in system in the acute phase of myocardial infarction with methodology partly developed in this laboratory

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SURVEY OF THE LITERATURE

I REMARKS ON THE HISTORY AND CHEMISTRY OF THE KININ SYSTEM

In 1926-28 Frey and co-workers observed that human urine contains a substance that produces a prolonged fall in arterial blood pressure in the dog when injected intravenously Kraut Frey and Werle found a similar vasodepressor substance in human blood (1928) and in pancreas (1930) and assuming these substances to be identical named the principle KALLIKREIN (Gr kallikreas = pancreas)

Werle Götze and Keppler discovered (1937) that kallikreins act indirectly by splitting off a pharmacologically active substance from a precursor present in blood This substance was named KALLIDIN by Werle and Berek (1948) At the same time Rocha e Silva Beraldo and Rosenfeld (1949) described the release of an active peptide from a plasma globulin fraction by trypsin and snake venoms This peptide lowered blood pressure and also caused a slow contraction of the guinea pig ileum Because of the slow response of the gut the substance was named BRADYKININ

Soon thereafter it was shown that bradykinin and kallidin are derived from the same substrate (Werle and Berek 1950) Later kallidin was found to be lysylbradykinin (Pierce and Webster 1961) Bradykinin was isolated from ox blood by Elliot Lewis and Horton (1960) and from human plasma by Hamberg (1962) and synthesized by Boissonnas Guttmann and Jaquenoud (1960)

Bradykinin kallidin and another naturally occurring analogue met lys bradykinin are derived from the same precursor KININOGEN by various KALLIKREINS (kininogenases) Met lys bradykinin has not yet been detected in human plasma (Habermann 1970) The three peptides brady

Bradykinin is a nonapeptide with an amino acid sequence as shown in Fig 1 In plasma kallidin is quickly converted to bradykinin by aminopeptidases (Webster and Pierce 1963)

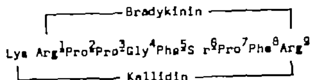


Fig 1 The amino oid sequence of human plasma kinins

The activation sequence of the human plasma kinin system (Fig 2) eventually leading to the activation of bradykinin involves a series of enzymes The sequence begins with the activation of the Hageman factor (coagulation factor XII) and continues through stages which have so far been only partly explained until plasma prekallikrein is converted to active kallikrein

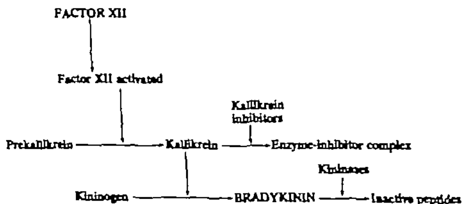


Fig 2 The activation eq ence of the plasma kallikrein kinin system

Margolis (1958) noted that glass contact results in release of kinins in human plasma and showed that this happens only in the presence of Hageman factor Later studies have confirmed that Hageman factor is essential to kinin formation (Webster and Ratnoff 1961 Colman et al 1969,b) In addition to glass there are several other substances and factors which have been pointed out as activators of Hageman factor <u>in vitro</u>: kaolin (Margolis 1963) collagen (Niewiarowski et al 1965) sebum (Nossel 1966; Ogston et al 1969) chondroitin sulfate (Moskowitz

SURVEY OF THE LITERATURE

I REMARKS ON THE HISTORY AND CHEMISTRY OF THE KININ SYSTEM

In 1926-28 Frey and co-workers observed that human urine contains a substance that produces a prolonged fall in arterial blood pressure in the dog when injected intravenously Kraut Frey and Werle found a similar vasodepressor substance in human blood (1928) and in pancreas (1930) and assuming these substances to be identical named the principle KALLIKREIN (Gr kallikreas = pancreas)

Werle Götze and Keppler discovered (1937) that kallikreins act indirectly by splitting off a pharmacologically active sub tance from a precursor present in blood This substance was named KALLIDIN by Werle and Berek (1948) At the same time Rocha e Silva Beraldo and Rosenfeld (1949) described the release of an active peptide from a plasma globulin fraction by trypsin and snake venoms This peptide lowered blood pressure and also caused a slow contraction of the guinea pig ileum Because of the slow response of the gut the substance was named *BRADYKININ*

Soon thereafter it was shown that bradykinin and kallidin are derived from the same substrate (Werle and Berek 1950) Later kallidin was found to be lysylbradykinin (Pierce and Webster 1961) Bradykinin was isolated from ox blood by Elliot Lewis and Horton (1960) and from human plasma by Hamberg (1962) and synthesized by Boissonnas Guttmann and Jaquenoud (1960)

Bradykinin kallidin and another naturally occurring analogue met lys bradykinin are derived from the same precursor KININOGEN by various KALLIKREINS (kininogenases) Met lys bradykinin has not yet been detected in human plasma (Habermann 1970) The three peptides brady kinin kallidin and met lys bradykinin are now known as *PLASMA KININS*

that HMW-kininogens are more susceptible to the action of plasma kallikreins which provides a potential control mechanism against direct bradykinin release (Colman 1974) Immunologically pure human kininogen was prepared by Hamberg and co-workers (Hamberg and Tallberg 1972; Hamberg et al 1975)

Active kinins are split very rapidly to inactive peptides by kinin destroying enzymes KININASES There are two main locations for the inactivation of circulating kinins plasma itself (Erdős 1961 Erdős and Sloane 1962) and the lungs (Ferreira and Vane 1967), which were shown to inactivate 80% of the injected bradykinin by one passage of blood Because of the rapid inactivation the half life of bradykinin is only 30-40 seconds first shown by Saameli and Eskes (1962)

At present two kininases are considered to account for the total kininase activity of plasma kininase I and kininase II Kininase I (arginine carboxypeptidase) (Erdős 1961) is primarily responsible for the hydrolysis of plasma kinins by removal of the C terminal arginine Kininase II (peptidyl dipeptidase) (Yang and Erdős 1967) hydrolyzes the pro^7 phe^8 bond of bradykinin From recent studies it is evident that kininase I functions mainly in plasma while kininase II is the final terminator of kinin function in tissues especially the lungs (Erdős 1976) It has been shown that kininase II is identical with angiotensin I converting enzyme which is known to function mainly in the lungs (Yang et al 1971)

II RELATIONSHIP OF THE PLASMA KININ SYSTEM WITH OTHER PROTEOLYTIC ENZYME SYSTEMS

The activation of Hageman facto initiates not only the plasma kinin system but at least three other proteolytic enzyme systems in blood i e the complement coagulation and fibrinolytic systems (see Ratnoff 1974 Colman 1974) In addition to their activation by Hageman factor all these systems have in common that a multitude of steps leads to the final active products intrinsic amplification several feedback mechanisms and finally common enzyme inhibition between complement kinin and fibrinolytic systems by C I esterase inhibitor (Ratnoff 1974) and coagulation- kinin and fibrinolytic systems by alpha 2 macroglobulin (Barrett and Starkey 1973)

It is noteworthy that activation of the plasma kinin system is further accelerated by plasmin, which deg ades activated Hageman factor to the so called prekallikrein activators (PKA) (Kaplan and Austen 1971)

et al 1970) platelets (Walsh 1972) and urate crystals (Kellermeyer and Breckenridge 1965) among others

In general activators carry a negative charge (zeta potentials) and lose their activity after their negative potentials are neutralized (Haanen et al 1961 Eisen 1964 1969) Hageman factor activation has been demonstrated also by antibody antigen aggregates (Movat and DiLorenzo 1968) These as well as collagen may be important in the activation process in certain disease states in vivo

Kallikreins are ubiquitous in the body and can be divided into tissue and plasma kallikreins In the submaxillary gland (Werle and von Roden 1936) and in the kidney (Frey 1926) the kallikreins are stored in an active form It has been shown that urinary kallikrein is identical with kidney kallikrein (Nustad 1970) Other tissue kallikreins are inert precursos molecules for which the activation mechanism has not yet been identified

Compared with tissue kallikreins (mol wt 24 000 36 000) human plasma kallikrein is of higher molecular weight (approx 100 000) and differs from them both physicochemically and immunologically It is synthesized as an inactive precursor PREKALLIKREIN by the liver (Werle et al 1955 Eisen and Vogt 1970) Plasma kallikrein liberates bradykinin and tissue kallikreins kallidin when acting on kininogen precursors (Webster and Pierce 1963 Habermann and Blennemann 1964)

Kallikreins were thought to be highly specific enzymes with only one natural substrate kininogen (Schachter 1969) but it now appears that kallikreins not only act as kininogenases but also play a role in other proteolytic mechanisms in plasma (see p 9)

Human plasma contains several KALLIKREIN INHIBITORS Ever since the discovery of kallikrein its action has been known to be partly inhibited (Kraut et al 1933) by an inhibitor in plasma which has later been shown to be identical with C 1 esterase inhibitor Other inhibitors of plasma kallikrein are alpha 2-macroglobulin alpha 1 antitrypsin and in the presence of heparin antithrombin III (Kagen et al 1963 Harpel 1970 McConnel 1972 Colman 1974 Harpel 1976)

It has been suggested that human plasma contains at least two classes of kininogens (see Habermann 1970) which are produced by the liver The first class includes the so called low molecular weight (LMW) kininogens I and II with a molecular weight of approximately 50 000 (Pierce and Webster 1966) In these two low molecular weight kininogens the bradykinin sequence of amino acids is located in different parts of the molecule The so called high molecular weight (HMW) kininogens (mol wt. approx. 200 000) are considered to be polymers of either of the two LMW kininogens (Colman et al 1971) They account for about 20% of the total [illegible] (Jacobsen and Kriz 1967) It appears

Despite the above mentioned observations no definite physiological roles may as yet be ascribed to the plasma kinin system

2 OVERALL CARDIOVASCULAR EFFECTS OF THE KININS

It has been claimed that the kinins possibly exert a direct positive inotropic action on the myocardium in vivo (Montague et al 1963 Reichgott and Melmon 1970) although this has recently been questioned (Hashimoto et al 1977) It is difficult to distinguish the reflex sympatho-adrenergic activity as a consequence of hypotension from direct effects of the peptides

The effect of bradykinin on vascular tone in vivo depends on the nature of the vessel being investigated on the species on the dose of the peptide and especially on interaction with other endogenous vasoactive substances

Large doses of injected bradykinin release catecholamines through stimulation of adrenal medulla (Feldberg and Lewis 1964) but smaller doses act indirectly through baroreceptor reflexes (Mason and Melmon 1965; Staszewska Barczack and Vane 1967) Conversely epinephrine and norepinephrine seem to decrease plasma kininogen (Erdös 1961 Castania, and Rotschild 1974) Nevertheless after epinephrine injection plasma kinin level does not increase but there is an increase in kininase activity (see Sicuteri 1970) The tendency of kinins to release catecholamines has led to the suggestion (Collier 1966) that the release is a protection mechanism of the body against systemic effects of the liberated kinins from the site of injury

It has also been shown that intravenous administration of bradykinin to man results in serotonin (5-hydroxytryptamine 5-HT) liberation (Peltola 1972) and there is evidence that kinins can cause release of histamine (Melmon and Cline 1967) Conversely intravenous injection of histamine or histamine liberator 48/80 in man causes a decrease in plasma kininogen (see Sicuteri 1970 b)

Intravenous injection of bradykinin to mammals including man usually results in systemic arterial dilatation which has been thought to be a direct action of bradykinin (see Haddy et al 1970) In almost all species studied bradykinin dilates the majority of arterioles including the coronary arteries (see Brecher and Brotmann 1970)

The effects of bradykinin on postcapillary vasculature and pulmonary vasculature are varied Recently it has been suggested that

In the conversion of inactive Hageman factor to active form plasma kallikrein itself is even more potent than plasmin through a positive feedback mechanism which also confirms the intimate relationship between the plasma kinin system and coagulation and fibrinolytic systems (Kaplan et al 1976) Thus the role of kallikreins is not limited to their action as kininogenases

III PLASMA KININ SYSTEM IN PHYSIOLOGY AND PATHOLOGY

1 POSSIBLE PHYSIOLOGICAL ROLES

Because of their widespread distribution and their remarkable potency the kinins have been thought to play a significant role in normal physiology in mammals including man Speculations on their possible function as chemical regulators of the blood flow of various organs are numerous It has been suggested that the kinins are regulators of functional hyperemia in salivary pancreatic tongue and sweat glands (Hilton and Lewis 1956 Fox and Hilton 1958 Lewis 1967) Melmon et al (1968) supported by experimental work by Campbell et al (1968) and later by Assali et al (1971) have suggested that the plasma kinin system is responsible for the rapid circulatory changes at the time of birth resulting in conversion of the fetal circulation to the adult circulatory pattern

It has also been suggested (Furuyama 1966) that the kinins act to regulate renal function In normal human subjects infusion of bradykinin enhances renal blood flow decreases glomerular filtration rate and increases urinary excretion of sodium (Webster and Gilmore 1964 Nasjletti et al 1975) It is possible that the renal effects of the kinins are mediated through the action of prostaglandins (McGiff et al 1972 McGiff and Nasjletti 1976)

Furthermore activation of the plasma kinin system during exercise has been mentioned by Hilton and Lewis (1955) Fox and Hilton (1958) and Uchida and Ueda (1969) Malofiejew et al (cited by Lantsberg et al 1973) found a smaller increase in blood kallikrein activity during exercise in physically trained persons than in non trained ones Lantsberg et al (1973) confirmed this finding and concluded that the blood kinin system evidently represents one of the humoral mechanisms governing the adaptation of the cardiovascular system to various conditions Malofiejew (1973) has also suggested that the plasma kinin system is activated during the process of labor

acute pancreatitis (Blomquist and Hamberg 1969; Sipilä 1977) postgastrectomy dumping syndrome (Wong et al 1974) allergic disorders (see Colman et al 1971) transfusion reactions (see Colman et al 1971) joint inflammation (see Webster and Maling 1970), and headache in migraine and subarachnoid hemorrhage (see Sicuteri 1970) In chronic alcoholic liver disease the synthesis of prekallikrein by the liver is reduced (Wong et al 1972) A 30-60% decrease in the normal kininogen level was shown to occur in plasma samples after thrombolytic treatment of deep venous thrombosis by streptokinase (Hamberg 1969)

It has been suggested that there is a connection between the vasodilator effects of the kinins and their effect on renal handling of sodium and water and the regulation of both normal and pathologic blood pressure Streeten et al (1972) described an orthostatic syndrome probably caused by impaired destruction of circulating bradykinin In patients with essential hypertension decreased excretion of urinary kallikrein has been observed (Elliot and Nuzum 1934 Margolius et al 1971)

The participation of the plasma kinin system in acute myocardial infarction has been under investigation by several groups (see p 15)

There are at least four hereditary disorders in which a lack of a component of the plasma kallikrein-kinin system has been observed Lack of C 1 esterase inhibitor which is also the principal kallikrein inhibitor in plasma has been detected in hereditary angioneurotic edema (Landerman et al 1962; Donaldson and Evans 1963) The absence of Hageman factor first described by Ratnoff and Colopy (1955) is an asymptomatic trait but may lead to disturbances in the activation of several proteolytic enzyme systems in plasma (Ratnoff 1974) Another clotting deficiency the Fletcher trait has been identified as being due to the absence of plasma prekallikrein (Wuepper 1973 Weiss et al 1974) Recently a hereditary disorder with a blood clotting deficiency in vitro has been recognized by three groups and identified by eponyms as Fitzgerald Williams and Flaujeac traits The missing factor is believed to be a high molecular weight kininogen These findings suggest that obviously also kininogen molecule plays a role in blood clotting (Waldmann and Abraham 1974; Colman et al 1975; Wuepper et al 1975)

the different action of bradykinin on arterioles and venules is mediated through prostaglandin release (Terragno et al 1975) Accordingly bradykinin releases the vasodilator prostaglandin E from the arteries but liberates the vasoconstrictor prostaglandin F from the veins The fact that indomethacin a known prostaglandin synthesis inhibitor blocks the vasodilator effect of bradykinin in the isolated perfused rabbit heart (Needleman et al 1975) further confirms this hypothesis

The effect of bradykinin on blood pressure is biphasic After the initial fall in pressure a secondary pressor phase often overshooting the control values is seen (see Haddy et al 1970) It has been shown that the pressor response is mediated via both central and peripheral sympathetic reflexes (see Haddy et al 1970) After the finding of the identity of angiotensin I converting enzyme and kininase II (Yang et al 1971) there has been increasing interest in their possible regulatory function on the plasma concentration of angiotensin II and bradykinin and regulation of normal blood pressure (see Mersey et al 1977)

The kinins increase capillary permeability to fluid and proteins The action of increasing vascular permeability after intradermal injection of bradykinin was first shown by Holdstock et al (1957) in guinea pigs and later observed in man (Herxheimer and Schachter 1959) It has been suggested that the permeability increase is a purely mechanical phenomenon related to passive distension of the venules (Rowley 1964) However more recently it has been shown by Ferreira (1974) that prostaglandin E enhances the effect of bradykinin on capillary permeability and thus bradykinin might be a mediator of permeability increase through the release of prostaglandins

3 KININS IN PATHOPHYSIOLOGY

The first clinical disorder in which kinins were suspected to play a significant role was the carcinoid syndrome (Oates et al 1964) It is possible that kinin action is responsible for the carcinoid flush in this disease In different shock states including hemorrhagic anaphylactic tornique and endotoxin shock the kinin system has been thought to be activated (see Vogel and Zickgraf Rüdel 1970) Most evidence of the activation of the kinins in shock has been found in endotoxin shock

There is evidence of the activation of the plasma kinin system in

5 KININS AND PAIN

Bradykinin is among the most potent pain producing substances known causing pain when applied to the blister base in man (Armstrong 1957; Keele and Armstrong 1964) and pain and vasodilatation when injected into the brachial artery or into the carotid of man (Burch and dePasquale 1962 Sicuteri 1970) Intracoronary (Uchida et al 1971) and epicardial (Uchida and Murao 1974 Staszewska Barczack et al 1976) administration of bradykinin in dogs produces pseudoaffective nociceptive responses If before and during the injection or application of bradykinin a local circulatory arrest is produced the pain will be even more intense and prolonged (Sicuteri et al 1967)

It has been shown that bradykinin is released from the heart within minutes from the onset of hypoxia or ischemia (Furukawa et al 1969 Kimura et al 1973) Thus it is plausible that bradykinin possibly along with other substances released locally at the site of injury is responsible for the pain as suggested originally by Lewis et al (1929-31) and later by Guzman et al (1964) The place of kinins in the pathogenesis of sustained painful states has also been questioned since cutaneous pain responses to kinins in man show marked tachyphylaxis (Korton 1963) However if the kinins are responsible for the pain in ischemia there are a number of factors that may potentiate their action in stimulating the sensory nerve endings In circulatory arrest the distribution and removal of the peptide is limited With gradual lowering of local pH the action of kininases on bradykinin is greatly decreased (Edery and Lewis 1962)

It has been suggested that the release and accumulation of serotonin (5-HT) may sensitize pain receptors to bradykinin (Sicuteri 1967) Furthermore it has been suggested that prostaglandins in conjunction with bradykinin may be responsible for the potentiation of pain sensitation in ischemia (Staszewska Barczack et al 1976)

6 KININS AND MYOCARDIAL ISCHEMIA AND INFARCTION

In 1967 Sicuteri et al when determining plasma kininogen in 14 patients in the early phase of myocardial infarction found that plasma kininogen levels were decreased a phenomenon suggesting the activation of the plasma kinin system In 1968 Wiegershausen et al determined plasma kininogen in 24 infarction patients and found that the kininogen level decreased being

4 KININS AND TISSUE INJURY

Tissue injury brings about the four cardinal signs characteristic of the early stages of inflammation - pain vasodilation increased vascular permeability and accumulation of leukocytes - which are all known actions of the kinins (Elliot et al 1960 Konzett and Stürmer 1960 Lewis 1962)

In addition there are two other points that suggest the role of kinins in the inflammatory process First kinins together with other vasoactive substances have been detected at the site of local injury (Rocha e Silva and Antonio 1960 Rocha e Silva and Rosenthal 1961 Melmon et al 1967) Secondly there is evidence that proteolytic enzymes are activated during tissue injury (Beloff and Peters 1945 Ungar 1947) Moreover local conditions prevailing in inflamed tissue favor the formation and accumulation of the kinins The lowering of pH at the site of injury might be a contributing factor in the activation of the kinin system (Werle 1934 Frey et al 1950) The change in pH of the interstitial space of inflamed tissue reduces the capacity of kininases to inactivate kinins (Edery and Lewis 1962)

Thus it seems possible that an inflammatory response to tissue injury of any kind could be brought about by kinin formation Once initiated the inflammatory response might continue by virtue of continued kinin formation Prekallikrein and possibly kininogen could simply diffuse from the blood vessels to the injured area or the active kallikrein could be brought to the site by leukocytes which are known to accumulate in the inflamed area (Lewis 1962)

It seems however unlikely that inflammation is mediated through a single chemical agent since various other substances e g histamine serotonin and more recently prostaglandins (Willis 1969) have also been detected in the inflammatory area These substances also exhibit actions characteristic of inflammatory response So far the interrelationship between the different mediators in tissue injury induced inflammation is unclear

Myocardial infarction may be considered an inflammatory response to anoxia - and on the basis of the present knowledge of biochemical pathology it can be assumed that the role which proteases play in inflammation is in general similar to that during myocardial infarction (Haberland 1975)

elevated and inhibitory activity as well as kininogen decreased The changes in plasma prekallikrein and kallikrein inhibitory activity were associated with the severity of the infarction as judged by hemodynamic parameters

Kimura et al (1975) studied 23 cases of acute myocardial infarction of which 16 were survival and 7 non survival They determined plasma kininogen and bradykinin during the course of the disease They noted a decrease with minimum level on the second day in kininogen with a simultaneous increase in bradykinin They also found a significant correlation between the lowering of blood pressure and changes in the examined parameters Furthermore they observed a significant correlation between plasma kininogen decrease bradykinin increase and lowering of total peripheral resistance as well as increase of circulation time but not decrease of cardiac output. Unexpectedly they found that in the non-survival cases the bradykinin level was significantly lower than in the survival cases They concluded that the release of kinins at the local myocardial site may perhaps be a beneficial compensatory mechanism contributing towards survival

Golikov et al (1977) studied 50 patients with acute myocardial infarction with a fatal course and determined spontaneous BAEe-esterase (kallikrein) activity prekallikrein and kallikrein inhibitory activity as well as epinephrine and norepinephrine levels in the blood Spontaneous esterase activity was considerably increased and prekallikrein and kallikrein inhibitory activity decreased Raised catecholamine levels were also observed within 6 hours after the onset of the disease

Coronary artery ligation in dogs has been shown to cause a significant increase in bradykinin in parallel with a decrease in kininogen in the coronary sinus blood (Kimura et al 1973 Hashimoto et al 1977) These data support the hypothesis that bradykinin is produced and released from the site of myocardial injury

Aprotinin a serine esterase inhibitor capable of inhibiting kallikrein has been used in experimental models of myocardial injury after coronary artery occlusion in the dog (see Hilkens et al 1975 Diaz et al 1977) The results indicate that aprotinin has beneficial effects probably by changing the normal consequences of tissue damage (see Hassion et al 1975) There are also reports of beneficial effects of aprotinin in clinical myocardial infarction (see Sicuteri et al 1975)

lowest 48 hours after the onset and rising thereafter There was no difference in the kininogen levels of the patients in shock as compared with the other infarction patients There was no correlation between the maximal serum GOT activity and the minimum of the kininogen level

Dzizinskii and Kuimov (1972) found when studying 70 acute myocardial infarction patients a decrease in plasma kininogen especially when complicated by shock They noted also that in such patients the BAEe esterase (kallikrein) activity was characterized by a high variance of the individual values The trypsin inhibitory activity indicating the degree of kallikrein inhibition was found to be increased in all patients with coronary insufficiency and highest in the acute phase of myocardial infarction

Pitt et al (1970) observed that of 11 patients experiencing ischemia with angina or typical ST segment changes in electrocardiogram during pacing test seven showed activation of the plasma kallikrein system with increased spontaneous plasma TAMe-esterase (kallikrein) activity Using the same analytical methods Sicuteri et al (1972) found that there was no change in spontaneous TAMe esterase activity in 16 infarction patients but prekallikrein was found significantly decreased with a minimum on the 8th day after the onset of the symptoms In 1973 Kedra et al observed a decrease in plasma kininogen on the first and second days the decrease was greater in patients with marked hemodynamic disturbances No correlation was shown between the extensiveness of the infarction as judged on the basis of ECG changes and plasma kininogen level

In the same laboratory another effort was made to evaluate the role of the plasma kinin system in infarction by determining prekallikrein kininogen and kininase in 54 infarction patients (Kolber-Postepska 1975) No correlation was observed between the extensiveness of the infarction and the examined parameters Nor were there any differences in the changes in plasma prekallikrein between patients with hemodynamic disturbances and noncomplicated patients Kininogen and prekallikrein were at the lowest simultaneously and were normalized after two weeks Kininase activity in all patients was less than in the control and did not change in two weeks The author concludes that the reduced kininase activity in patients with myocardial infarction may prolong the presence of kinins in plasma and thus increase their biological activity

Gomazkov (1974) determined plasma spontaneous TAMe-esterase (kallikrein) activity prekallikrein and kallikrein inhibitory activity as well as plasma kininogen level in 20 patients with myocardial infarction Prekallikrein was at its lowest on the second day and returned to normal by the fifth day Spontaneous esterase activity was

MATERIAL

I PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

The investigation was carried out on 65 patients with acute myocardial infarction admitted to Helsinki University Central Hospital in two periods of time during the year 1976

Patients over 75 years of age alcoholics and patients who lived outside the Helsinki district were excluded Those patients were also excluded who died within two days of their arrival and those who arrived more than 48 hours after the onset of the acute symptoms or could not give the exact time of the appearance of the symptoms Otherwise the patients represent an unselected sample of acute myocardial infarction The patients were followed throughout the stay in hospital two weeks on the average and were asked on a control visit one month from the onset of the symptoms

The treatment of the patients was not influenced by the author and was in each case individually decided by the physician on duty 46 patients made a control visit after one month The age and sex distribution of the infarction patients is shown in Fig 3

All patients included belong to the first diagnostic category (Definite acute myocardial infarction) of the WHO classification (Ischaemic Heart Disease Registers Report of the Fifth Working Group WHO Copenhagen 1971)

OBJECTS OF THE PRESENT STUDY

The participation of the plasma kinin system in hemodynamic response and in pain in myocardial infarction has been suggested No clinical investigations so far published deal with all the essential components of the plasma kinin system Attempts to correlate changes in various components with the clinical picture and parameters are only a few and show considerable discrepancy

Thus it seemed desirable to obtain a more comprehensive view of the possible changes in the different components of the plasma kinin system and their relationship to one another during the evolution of the disease

The aim of the study is to answer the following questions

Does activation of the plasma kinin system occur in acute myocardial infarction as judged from the changes in plasma prekallikrein kallikrein kallikrein inhibitory activity kininogen and kininase activity as compared with control patients and what is the time course of these changes?

Do the changes correlate with the extent and severity of the infarction as judged

by serum maximal creatine kinase (CK) activity
by comparing transmural with non transmural infarctions and
- by clinical hemodynamic criteria?

- Do the changes in the plasma kinin system correlate with the duration of pain in acute myocardial infarction?

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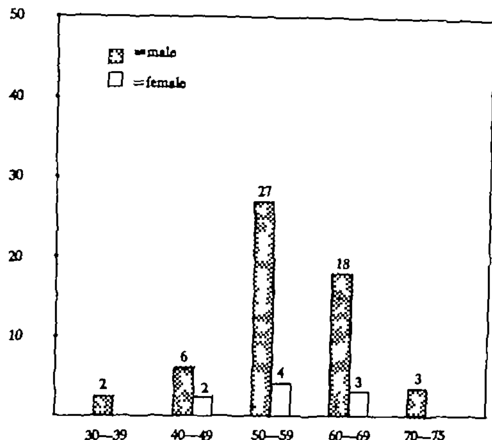


Fig 3 Age and sex distribution of the patients with acute myocardial infarction

II CONTROL PATIENTS

16 patients undergoing minor eye operations at the Clinic of Ophthalmology of Helsinki University Central Hospital constituted the control group This group was followed for four days in the hospital and they remained in recumbency during this time

The possibility of silent myocardial infarctions in the control group was excluded by daily determinations of serum total creatine kinase activity

The age and sex distribution of the whole patient material is shown in Table 1

Table I Age and sex distribution of the patient material of the study

Group	Number of patients	Age, years mean (median) range	Sex
Control patients	16	56.0 (60.0) 28 75	M 10 F 6
Myocardial infarction (AMI)	65	55.8 (55.0) 35 72	M 59 F 9

METHODS

I DEFINITION OF THE CLINICAL CONCEPTS

1 ACUTE MYOCARDIAL INFARCTION (AMI)

In this study the diagnosis of acute myocardial infarction was based on the clinical picture electrocardiographic changes indicative of myocardial necrosis and laboratory tests

Appearance of pathologic Q-wave in successive ECG recordings together with ST segment and T-wave changes indicated transmural injury whereas ST segment and T-wave changes alone were indicative of non-transmural (subendocardial) injury

All diagnoses were primarily made by the physicians in charge of the patients In all patients the serum total CK activity was determined on the first three days after admission Since it is often difficult to distinguish prolonged anginal attacks from mild forms of infarction the final differentiation of these borderline cases was based on detection of myocardial specific (Sobel et al 1972; Konttinen and Somer 1973) MB-isoenzyme of CK in serum during the first three days after admission

2 HEART FAILURE

Heart failure is defined as a condition in which the heart is unable to maintain an adequate cardiac output in relation to venous return or the needs of the tissues Acute heart failure may be subdivided into acute congestive heart failure and shock

by signs of venous congestion and venous hypertension behind the left ventricle In cardiogenic shock the clinical picture is characterized by severe systemic arterial hypotension with signs of inadequate tissue perfusion In acute myocardial infarction heart failure frequently has the characteristics of congestive heart failure and shock simultaneously

The bedside signs suggestive of congestive heart failure of left ventricular origin were as follows dyspnea at rest orthopnea tachypnea attacks of wheezing in the absence of pulmonary disease rapid forced respiration and moist rales over the lung fields and prolonged sinus tachycardia of over 110 beats per minute Patients were considered to have clinical pulmonary congestion only if there was both radiographic and auscultatory evidence

Clinical signs of congestive heart failure of right ventricular origin were as follows enlarged often tender liver peripheral sacral and ancle edema without a local cause and rise of jugular venous pressure when it was clearly observable

The grade of peripheral hypoperfusion was assessed by the presence of decreased temperature of the skin pallor cyanosis restlessness confusion decreased urinary output and rapid feeble pulse with systemic arterial hypotension of 100 mmHg or below

In this study the patients were classified into three rigorously defined subgroups according to clinical hemodynamic criteria The subdivision was performed by an expert cardiologist according to clinical records which in each case had been completed bedside by the author

II CLINICAL EXAMINATION OF THE PATIENTS AND SAMPLE COLLECTION

The patients included in the present series were examined by the author on the same days as the blood samples were taken for the various analyses of the study In the beginning of the follow-up a history of earlier cardiovascular and other diseases was taken and the onset of the present symptoms was carefully recorded In clinical examination particular attention was paid to various manifestations such as paradoxical pulsation pericardial friction rub and atrial and ventricular gallops which may give diagnostic support in suspected myocardial infarction In addition careful examinations were performed to detect signs of congestive heart failure and/or signs of decreased peripheral perfusion as described in the preceding chapter

Conventional 12 lead electrocardiograms were taken of all patients during the first days after admission The routine laboratory tests depended on whether the patient was admitted to the intensive care unit or transferred to an ordinary ward Anteroposterior roentgenograms were taken daily of the patients in the intensive care unit. Moreover heart function was monitored and central venous pressure and/or pulmonary wedge pressure measured during the stay in the unit

The first blood sample was taken on admission and the subsequent samples on the 2nd 3rd 4th and 6th 8th days after the onset of the symptoms An additional sample was taken after one month on a control visit Of the control patients samples were taken on admission the second day and on the third or the fourth day in hospital

For the assay of the components of the kallikrein system citrated plasma was prepared as follows 9 ml of venous blood from antecubital fossa was taken with a siliconized needle into a plastic tube containing 1 ml of 3 8 % sodium citrate and mixed After centrifugation at 2000xg for 15 minutes at room temperature the plasma samples were frozen at 20^{0}C in several aliquots

For the assay of kininogen and kininases an additional sample of 10 ml of venous blood was taken through the same needle into a plastic tube containing 500 units of heparin (Heparin Medica) mixed and centrifuged The plasma was prepared as described later for the assay of kininogen and kininases

Serum total protein and serum total creatine kinase activity and MB isoenzyme activity determinations were carried out on serum samples taken through the same needle

The samples in the intensive care unit were taken through a central venous catheter through which 10 ml of blood had been passed before collecting There were no differences in the measured components as ascertained by several samples taken by both means whether the samples were collected via CVP catheter or from the brachial veins

It as also ascertained that freezing of the plasma samples once did not destroy the acti ities measured when the final assays were carried out within 5 months from the collection of the samples

III METHODS OF ASSAY

The acti ation of the plasma kinin system should lead to consumption and consequent decrease of plasma prekallikrein and kininogen with a

by signs of venous congestion and venous hypertension behind the left ventricle In cardiogenic shock the clinical picture is characterized by severe systemic arterial hypotension with signs of inadequate tissue perfusion In acute myocardial infarction heart failure frequently has the characteristics of congestive heart failure and shock simultaneously

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II CLINICAL EXAMINATION OF THE PATIENTS AND SAMPLE COLLECTION

The patients included in the present series were examined by the author on the same days as the blood samples were taken for the various analyses of the study In the beginning of the follow-up a history of earlier cardiovascular and other diseases was taken and the onset of the present symptoms was carefully recorded In clinical examination particular attention was paid to various manifestations such as paradoxical pulsation pericardial friction rub and atrial and ventricular gallops which may give diagnostic support in suspected myocardial infarction In addition careful examinations were performed to detect signs of congestive heart failure and/or signs of decreased peripheral perfusion as described in the preceding chapter

also hydrolyzed but more slowly the rates decreasing in the above order (Webster and Pierce 1961)

Mainly BAEe and TAMe have been used as substrates in kallikrein assays The assays based on BAEe-hydrolysis all use BAEe in a final concentration of about 1 mM which is far below the Km of plasma kallikrein reported at 13 6 mM (Colman et al 1971) and therefore significantly limits the accuracy of these assays Consequently of the esterolytic methods that of Colman et al (1969) using TAMe has proved to be most useful especially since it allows simultaneous measurement of spontaneous esterase (kallikrein) prekallikrein and kallikrein inhibitory activity

The assay is based on the observations that citrated normal human plasma collected without exposure to glass contains extremely low levels of spontaneous arginine esterase activity the increase of esterase activity after exposure to kaolin results primarily from the activation of plasma prekallikrein and that the rapid fall in arginine esterase activity after maximal activation is due to plasma kallikrein inhibitors (Colman et al 1969 b)

The substrate used is N-tolyolsulfonyl L arginine-methylester (TAMe) Its hydrolysis liberates methanol which is measured according to the original method of Siegelman et al (1962) The time course of the activation by kaolin is typical A maximum in normal plasma is obtained in 1 2 minutes with a decline thereafter to a level which remains the same for several minutes (Fig 4)

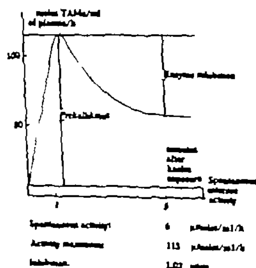


Fig 4 The activatio curve of the plasma kal ikrein system Co st ted from the mea of 48 measure nts o 16 c trol pati nts The c rve repr se ts r red pl sma sterase activity at different time intervals ft r kaoli acti atio at z ro

concomitant rise in plasma kallikrein and bradykinin Changes are also expected in kallikrein inhibitory as well as kininase activities

Demonstration of elevated free bradykinin alone certainly suggests its participation in a pathological process but hardly gives a reliable picture of the state of the plasma kinin system at a given moment In addition measurement of plasma free bradykinin has so far appeared extremely unreliable because of the short biological half life of the peptide and because of the problems of specificity and relative insensitivity of the assay methods available

Both bioassay and radioimmunoassay have been used in measuring plasma free bradykinin (see Trautschold 1970) A common problem for both is the difficulty in the sample collection due to the instability of bradykinin Bioassay is unreliable because of the potentiating factors in plasma (Louhija and Sipilä 1972) and it usually lacks the necessary sensitivity The unreliability of the methods for free bradykinin determination is evident from the fact that various authors have reported normal plasma bradykinin levels varying from 0 2 ng/ml (Zacest and Mashford 1967 Mashford and Roberts 1972) to 3 ng/ml (Talamo et al 1969)

With the radioimmunoassay for bradykinin developed in this laboratory (range of measurement 1 20 ng BK/sample) no free bradykinin activity in normal human plasma could be detected Thus plasma free bradykinin measurement was not attempted in this study but evidence of possible activation of the plasma kinin system was sought by measuring those components which are more stable and for which there exist more reliable methods of assay

I PLASMA KALLIKREIN PREKALLIKREIN AND KALLIKREIN INHIBITORY ACTIVITY

Plasma kallikrein (EC 3 4 21 8) has been assayed mainly by two approaches by means of bioassay which measures the kinin released by the proteolytic action of kallikrein and by chemical methods based on the esterolytic properties of kallikrein Because of the known disadvantages of bioassay chemical methods using synthetic basic amino acid esters notably arginine derivatives as substrate have been more widely preferred Of the synthetic esters commercially available all kallikreins hydrolyze N benzoyl L arginine-ethylester (BAEe) most effectively N benzoyl L arginine-methylester (BAMe) (Webster and Pierce 1961) N tolyolsulfonyl L arginine-methylester (TAMe) and N acetyl L tyrosine-ethylester (ATEe) are

COMMENTS

The method is not specific for free kallikrein since a number of other proteolytic enzymes e g plasmin trypsin thrombin and C 1 esterase will also hydrolyse TAMe (Colman et al 1969) When elevated spontaneous esterase activity is encountered a further characterization of the enzyme profile is necessary

For plasma prekallikrein this method is reasonably specific since it has been shown that rising esterase activity after kaolin activation is due to plasma prekallikrein (Colman et al 1969 b)

This method also allows the measurement of total kallikrein inhibitory activity of plasma Activated plasma kallikrein has been shown to bind to alpha 2-macroglobulin (Harpel 1970) Since the complex bound kallikrein can still be measured with synthetic ester substrates (Barrett and Starkey 1973) possibly bound activity is included in the present measurements

Since the activation curve rises very rapidly after kaolin exposure (Fig 4) it is important to try to come as close to the activity maximum as possible In this laboratory it was found that especially with pathological plasma the kaolin activation time may be significantly delayed and thus with only one sample taken e g at 1 minute as suggested by Colman et al the maximum may be missed Therefore we made activity determinations at 1 minute 1 5 minutes and 2 minutes

The normal values obtained (Fig 4) agree well with the normal values of Colman et al (1969) spontaneous esterase activity 7 μmoles/ml/h activity at one minute (maximum) 97 μmoles/ml/h and inhibitory acti ity 1 00 IU

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Plasma kininogen has usually been measured by bioassay of bradykinin totally liberated by trypsin from heat acid denatured plasma (Diniz and Carvalho 1963) Along with the usual disadvantages of bioassay the most se ious drawback of this method is the possible involvement of bradykinin potentiating factors (Hamberg 1968 Aarsen 1968 Louhija and Sipila 1971)

A method for kininogen determination based on radioimmunoassay of trypsin liberated bradykinin has recently been introduced (Sipilä and Louhija 1976) This method is more suitable for serial determinations than bioassay and it gives results that are in good agreement with those

which represents the spontaneous esterase (kallikrein) activity Further samples were taken at 1 1 5 2 and 5 minutes The peak value minus spontaneous activity represents total pre kallikrein and enzyme inhibition can be calculated from the value after levelling off

Marked glass tubes each containing 41 9 mg of TAMe (N^a Tosyl L-arginin-methylesterhydrochlorid Merck) in 2 ml of 0 1 M sodium phosphate buffer pH 7 6 in 0 15 M NaCl were placed in an ice bath

For the measurement of spontaneous arginine esterase (kallikrein) activity 0 1 ml of the first test sample and 0 1 ml of the buffer were added with plastic pipette to the first TAMe tube in the series For the measurement of prekallikrein and kallikrein inhibitory activity equal volumes of kaolin (Kaolin Baker) suspension (10 mg/ml) in buffer and of test sample were mixed in plastic tubes and incubated at 25°C in a water bath At the end of 1 minute 1 5 minutes 2 minutes and 5 minutes aliquots of 0 2 ml were pipetted over and immediately mixed in respective TAMe tubes The tubes were then withdrawn from the ice bath and placed in a water bath at 37°C At 1 minute and at 31 minutes aliquots of 1 ml were removed from each tube and added to 0 5 ml of 15% trichloroacetic acid and centrifuged

0 5 ml of the supernatant was removed and placed in a separate test tube containing 0 1 ml of 2% potassium permanganate After mixing vigorously for 1 minute 0 1 ml of 10% sodium sulfite was added and mixed 4 ml of 0 2% chromotropic acid in 65% sulfuric acid was added and mixed thoroughly The samples were placed in a boiling water bath for 15 minutes and thereafter allowed to cool

Each hydrolyzed (31 minutes) sample was measured against its own nonhydrolyzed (1 minute) blank set at zero at 580 mμ in a Beckman DU spectrophotometer at 25°C Using weighed amounts of methanol as standards it was found that an absorbance of 0 100 is equivalent to 36 5 μmoles of methanol released or TAMe hydrolyzed per milliliter of plasma per hour

Spontaneous esterase activity and prekallikrein are expressed as μmoles of TAMe hydrolyzed/ml of plasma/hour The kallikrein inhibitory activity can be expressed as follows 1 U of kallikrein inhibition is that amount of inhibitory activity that at 5 minutes gives 50% inhibition of the maximum value The number of units was computed from a calibration plot of $\log \frac{\text{activity at 5 minutes}}{\text{activity maximum}}$ vs inhibitory units The standard deviation of the mean of 14 prekallikrein measurements obtained from the same sample was 1 9 %

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Bradykinin was liberated from plasma kininogen according to the method of Diniz et al (1961) by trypsin incubation of the heat acid denatured plasma samples Bradykinin immunogen was prepared by coupling bradykinin to human serum albumine The radioimmunoassay procedure was a slight modification of that of Talamo et al (1968)

0 2 ml of heparin plasma was added to 1 8 ml of 0 2% acetic acid in plastic tubes and heated in boiling water bath for 30 minutes The pH of the mixture was adjusted to 7 4 7 8 by adding 0 1 N NaOH and buffered to pH 7 8 at 37°C (Astrup pH-meter Radiometer Copenhagen) by adding 0 5 ml of 0 2 M Tris buffer 200 µg of crystallized trypsin in 0 1 ml of saline was added and the mixture was incubated for 30 minutes at 37°C in a water bath The incubation was stopped by adding 5 ml of boiling ethanol and the mixture was further incubated for 10 minutes at 70°C The mixture was cooled centrifuged and the supernatant taken to dryness in a siliconized 100 ml round bottomed flask under reduced pressure (Rotavapor Buchi) and at a temperature of 35°C The dried precipitate was stored at 20°C until assay For the assay the precipitate was dissolved in 2 ml of veronal acetate saline-buffer with 1% gelatine which is the best stabilizer of weak bradykinin solutions

Bradykinin immunogen was prepared by coupling bradykinin to human serum albumin using water-soluble carbo-di imide 12 5 mg of human serum albumin (Kabi) was dissolved in 0 5 ml of distilled water 30 mg of bradykinin triacetate (Sigma) was added and dissolved and followed by 450 mg of 1 ethyl 3 (3 dimethyl aminoprolyl) carbo-di-imide HCl (Ott Chemical Company) The solution was mixed kept in ice bath for 48 hours at +4°C 4 ml of distilled water was added and the solution was thoroughly mixed with 4 ml of Freund s complete adjuvant (Difco) The immunogen was injected intramuscularly into all four legs of the rabbits to be immunized One rabbit out of fifteen produced a usable antiserum The antiserum was used in a dilution of 1 100 Using this solution the ratio of the radioactivity bound to antibody in absence of unlabelled bradykinin was about 40%

A radio-labelled tracer was prepared according to Greenwood et al (1963) 20 µl of 0 5 M phosphate buffer pH 7 0 50 µl of tyrosine-bradykinin solution (0 5 mg/ml) (New England Nuclear) and 25 µl of Chloramine-T (5 mg/ml) (Merck) were added to about 2 mCi (^{125}I) sodium iodide (IMS 30 The Radiochemical Centre Amersham) After 45 seconds 100 µl of sodium metabisulfite (2 5 mg/ml) (Merck) was added and immediately thereafter 5 µl of potassium iodide solution (20 mg/ml in 2 N acetic acid) (Merck) The solution was purified from unbound iodine by chromatography on a 4 ml Dowex column (Dowex 1x8 Cl 200 400 mesh) (Fluka) in a disposable plastic pipette The elution was made using water The fraction (0 5 ml) containing the top activity of bound iodine was diluted to get a working solution of 2000 counts per minute per 5 µl

The radioimmunoassay was carried out at room temperature as follows Throughout the procedure all solutions contained 1 % of gelatine 20 µl of unknown or standard bradykinin solution (bradykinin triacetate Sigma) 5 µl of (^{125}I) tyr^{0} bradykinin working solution and 5 µl of 1 100 dilution of antiserum all in veronal acetate buffered saline pH 7 4 (veronal 1 47 mg/ml and acetate 9 7 mg/ml in 0 13 M saline) were added in this order into 1 ml conical plastic centrifuge tubes (Fischer) The amount of

non-specific binding of bradykinin to rabbit serum was controlled by including a tube of non immunized rabbit serum to each analysis. The incubation was carried out at room temperature for 1 hour which was found to be enough for optimal binding. At the end of incubation period 400 µl of dextran coated charcoal suspension was added. The mixture was allowed to stand for 10 minutes and was centrifuged and 100 µl of the supernatant was counted for radioactivity. A standard curve was plotted from 6 standard samples each time and the amount of bradykinin in duplicate unknown samples was derived from this curve.

The range of the assay lies between 1 and 20 ng of bradykinin in the sample. The standard deviation of the differences from the mean of 12 measurements obtained from the same sample was 2.5 % at the level of 65 % inhibition and 3.0 % at the level of 45 % inhibition. The interassay standard deviation was 7 % derived from 26 duplicate determinations.

COMMENTS

With this method the mean kininogen content in plasma of 26 normal individuals was 3.36 ± 0.096 (S.E.M.) µg of bradykinin/ml of plasma which is in agreement with the results of Hamberg (1969) 4.31 ± 0.067 (S.E.M.) µg of bradykinin/ml of plasma for total plasma kininogen of pooled human blood bank plasma using bioassay on the isolated guinea pig.

In the present study the results for plasma kininogen are expressed as µg of bradykinin/ml of plasma and µg of bradykinin/g of serum protein in order to eliminate the effects of any hemoconcentration or hemodilution (see Habermann 1970).

3. PLASMA KININASES

In this study plasma kininase (EC 3.4.12.7 EC 3.4.15.1) activity was determined by a method based on radioimmunoassay for bradykinin (Sipilä 1977).

Heparin plasma was diluted 10 to 1 by 0.6 M phosphate buffer pH 7.5. In a small plastic tube 0.9 ml of this solution was mixed with 600 ng of synthetic bradykinin (Bradykinin triacetate, Sigma) in 0.1 ml of phosphate buffer. Immediately after mixing the tube was incubated at 37°C in a water bath. Samples of 0.1 ml were taken after 2 minutes, 6 minutes and 10 minutes incubation. Samples were immediately mixed with an equal volume of phosphate buffer in plastic tubes kept in ice. The phosphate buffer in these tubes contained 0.003 M of disodium EDTA to stop the kininase activity.

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IV STATISTICS

Conventional statistical methods were used for the calculations of mean values and of S E.M The significance of difference between sample means was estimated by the two tailed student s t test and probabilities above 0 05 were considered non-significant Regression analysis of linear correlations was carried out according to the method of least squares

promptly (Yang and Erdös 1967) and 1 % of gelatine to preserve the bradykinin activity Unspecific binding of diluted plasma in the radioimmunoassay was monitored by adding to the analysis a control tube with mixture of diluted plasma and EDTA-gelatine phosphate buffer in equal amounts

The results were plotted on a graph and the activity of kininases was expressed in IU One mIU of kininase activity inactivates 1 06 µg of bradykinin per minute (Trautschold 1970) The standard deviation from 8 duplicate measurements of the same sample was 2 1 %

COMMENTS

Methods in which plasma is incubated with added amounts of synthetic bradykinin are not specific for a particular kininase The present method thus measures the total kininase activity in plasma

4 SERUM TOTAL CREATINE KINASE (CK) AND MB ISOENZYME

Serum total CK activity (EC 2 7 3 2) was determined from deep-frozen samples with Boehringer CPK test sets (Boehringer Mannheim West Germany) at 25°C The activity is expressed as IU/l The upper normal value is 50 IU/l

The MB isoenzyme activity was determined by the method of Somer and Konttinen (1972) Since the MB isoenzyme was used as a plus-or-minus test for detection of myocardial damage no quantification was performed

5 SERUM TOTAL PROTEIN

Serum total protein was determined by the biuret method (Weichselbaum 1946) from deep-frozen serum samples

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RESULTS AND DISCUSSIONS

I THE COMPONENTS OF THE PLASMA KININ SYSTEM IN ACUTE MYOCARDIAL INFARCTION

1 PLASMA KALLIKREIN PREKALLIKREIN AND KALLIKREIN INHIBITORY ACTIVITY

Table II shows the spontaneous TAMe-hydrolyzing (kallikrein) activity of citrated plasma in acute myocardial infarction and control groups There are no significant differences between the two groups and no significant changes during the follow up

Table II Spontaneous esterase activity (μ moles TAMe/ml of plasma/h) in control and acute myocardial infarction (AMI) (means and S.E.M.)

Group (N)	<24 h	24 48 h	48 96 h	6 8 d	30 d
Control (16)	5.3±0.23	5.8±0.24	6.1±0.24	—	—
AMI (65)	6.2±0.22	6.1±0.21	6.1±0.21	6.2±0.22	6.3±0.27

Fig 6 presents plasma prekallikrein in acute myocardial infarction and control groups There are no changes in the control group during the follow-up and the initial value of the infarction group does not differ from the control values In the infarction group plasma prekallikrein decreases after 24 hours from the beginning of the symptoms being at its lowest on the 3rd 4th day of the disease and rising thereafter The difference is statistically significant on the second day (t 2 602 df 79 p<0 01) third to fourth day (t 3 873 df 77 p<0 001) as compared with the respective control values and after a week (t 4 791 df 123 p<0 001) as compared with the initial value of the infarction

group as there are no control values at one week

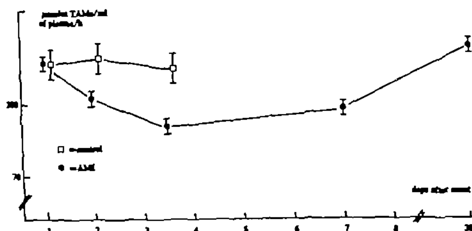


Fig 5 Plasma prekallikrein (means and S E M) in control nd a t myocardial infarction (AMI)

The kallikrein inhibitory activity is initially higher in the infarction group than in the control group The difference is statistically significant on the first day of the disease (t 1 975 df 77 p<0 05) The results are presented in Table III

Table III Kallikrein inhibitory activity (inhibitory units) in control and acute myocardial infarction (AMI) (means and S.E.M.)

Group (N)	<24 h	24-48 h	48-96 h	6-8 d	30 d
Control (16)	1.02±0.029	1.01±0.034	1.03±0.044	—	—
AMI (65)	1 14±0.028	1.06±0.025	1.03±0.024	1.03±0.034	1.09±0.026

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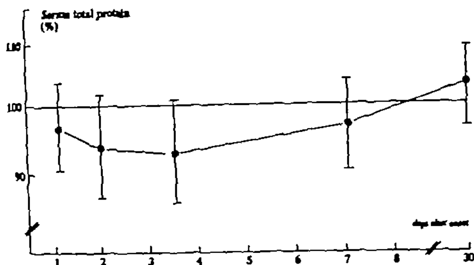


Fig 8 Serum total pr tein in the 65 infarction patients of the study (mea s and S D) The 100% line represents the co trol l el calculated from 48 measureme ts of the 18 control patients serum protein valu s One or two stars i dicate statistical ignificance at the 0 05 or 0 01 probability level respectively

It can be seen that kininogen reaches its minimum after 48 hours from the onset and returns to the control level in one week The statistical significances are as follows Kininogen (expressed as μg bradykinin/ml of plasma) as compared with the control on the first day t 2 075 df 77 p<0 05 on the second day t 2 910 df 78 p<0 01 on the third to fourth day t 3 211 df 77 p<0 001 Kininogen (expressed as μg bradykinin/g of serum protein) as compared with the control; on the first day t 1 650 df 77 p<0 05 on the second day t 3 819 df 78 p<0 05 on the third to fourth day t 1 896 df 77 p<0 05

Fig 9 shows the plasma kininase activity in 19 infarction patients at the time when plasma kininogen was lowest and at the time of recovery compared with the values of 10 control patients There are no differences between the groups

DISCUSSION

In previous reports both unchanged (Dzizinskii and Kulmov 1972 Sicuteri et al 1972) and elevated (Gomazkov 1974 Golikov et al 1977) spontaneous esterase (kallikrein) activities in myocardial i farction have been observed There are several factors that could explain the differing results It is possible that changes in plasma free

2 PLASMA KININOGEN AND KININASES

Plasma kininogen expressed as µg of bradykinin/ml of plasma is shown in Fig 6 and as µg of bradykinin/g of serum protein in Fig 7 It was observed that serum total protein decreases significantly during the course of the disease being lowest on the third to fourth day (Fig 8)

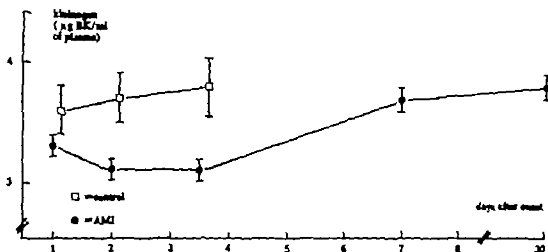


Fig 6 Plasma kininogen (expressed as µg BK/ml of plasma) in control and acute myocardial infarction (AMI) (means and S E M)

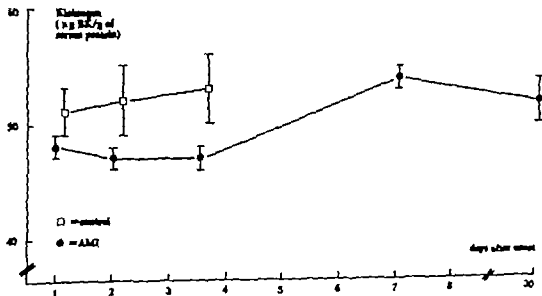


Fig 7 Plasma kininogen (expressed as µg BK/g of serum protein) in control and acute myocardial infarction (AMI) (means and S E M)

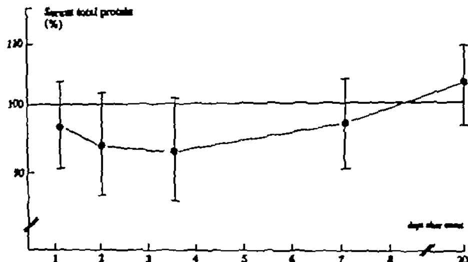


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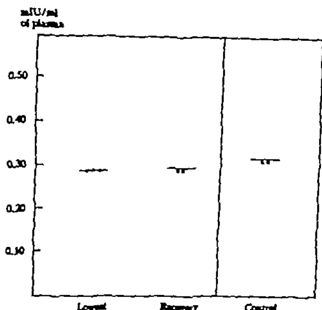


Fig 9 Plasma kininase activity in acute myocardial infarction on the day when plasma kininogen level was lowest and at the time of recovery compared with the control group

kallikrein take place very early and are only transient because of the continuously acting plasma kallikrein inhibitors It is also possible that changes are not observed owing to the relative insensitivity of the method On the other hand elevated esterase activity may also be due to other proteolytic enzymes in plasma

The observation of augmented kallikrein inhibitory activity during the very early stage of the disease may indicate an actual triggering of the activation of the plasma kinin system After the increase there is a gradual decrease Dzizinskii and Kuimov (1972) observed markedly elevated trypsin inhibitory activity in acute myocardial infarction Sicuteri et al (1975) noticed a gradual decrease in kallikrein inhibitor using the same method as has been used in this study The decrease paralleled the lowering of prekallikrein the maximum of the loss appearing on the 8th to 10th day of the disease

It is possible that the results obtained by Sicuteri et al (1975) i e the later appearance of the maximal prekallikrein decrease as compared with the present results as well as the decrease in kallikrein inhibitory activity is due to a methodological difference It was observed in this laboratory that with pathological plasma the activation time after kaolin exposure may be delayed beyond one minute Thus if the one minute sample is taken to represent prekallikrein the values will be too low Consequently since the five minute value is constant the inhibitory activity may also be misinterpreted

Plasma kininogen reaches its minimum after 48 hours and it is also normalized sooner than prekallikrein i e in one week This is in

good agreement with previous reports by others Since serum protein also decreases during the disease it is necessary to correct the kininogen values in proportion to serum protein It can be seen that the changes in plasma kininogen still remain significant after this correction (Fig 7.)

According to the present results there are no changes in plasma kininase activity during acute myocardial infarction No attempt was made in this study to activate possible latent kininases in plasma In addition it should be remembered that not only plasma but also the tissues especially the lungs are potential sites of kinin inactivation Kolber-Postepska (1975) observed a decrease in plasma kininase activity in patients with acute myocardial infarction The activity did not increase towards the recovery

II PLASMA PREKALLIKREIN AND KININOGEN AS RELATED TO MAXIMAL SERUM TOTAL CK ACTIVITY

Serum total CK activity was determined of all the patients in the infarction group on the first three days after admission Peak value of serum total CK appears within 16 to 30 hours from the onset of acute symptoms (Sobel et al 1972) Maximal serum total CK value within these time limits was taken to represent each patient s total CK maximum which was then compared with the maximal prekallikrein and kininogen decrease The results are shown in Fig 10 and Fig 11 The correlation is significant in both

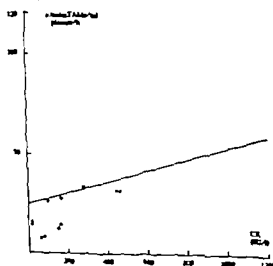


Fig 10 R lat o batwe n maximal plasma prekallikrein d cr s and ma imal s rum total CK otivity in ac te myocardial i fa ction (y 22 51 0 0317 r 0 4661 t 3 4722 p<0 01 N 38)

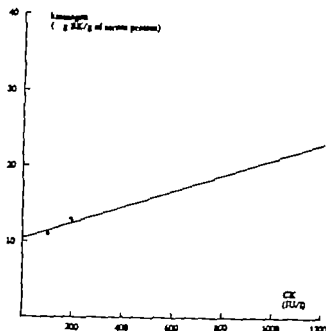


Fig 11 Relation between maximal plasma kininogen decrease (expressed in proportion to serum total protein) and maximal serum total CK activity in acute myocardial infarction (y 10 48 0 011x r 0 4365 t 2 829 p<0 01 N 36)

DISCUSSION

It is generally agreed that certain serum enzyme levels after myocardial infarction roughly correlate with infarct size (Nydick et al 1955 see Sobel et al 1972) In this study maximal serum total creatine kinase was compared with the changes in plasma prekallikrein and kininogen

The mean appearance time of the peak value of serum total CK activity in the group was 23 7 hours which is in good agreement with two other reports (Mathey et al 1974 Inoue et al 1977) 24 hours both The mean maximal total CK value at this time 369 IU/l is also in agreement with the results of other authors (Mathey et al 1974) 380 IU/l

Because intramuscular injections can cause a release of extracardiac CK (Meltzer et al 1970 Zener and Harrison 1974 Klein et al 1973) all patients who received intramuscular injections were excluded from CK-grouping For the same reason patients who had been resuscitated or defibrillated were also excluded (Konttinen et al 1969) The most severe hemodynamic group including 7 patients was also excluded since extracardiac CK release has also been reported in shock (Klein et al 1973)

The present results suggest that there is a correlation between the infarct size and the decrease in plasma prekallikrein and kininogen There is only one previous attempt in the literature to correlate serum enzyme changes with the plasma kinin system (Wiegershausen et al 1968) No correlation was found between the maximal serum GOT-activity and the minimum plasma kininogen level

III PLASMA KALLIKREIN INHIBITORY ACTIVITY PREKALLIKREIN AND KININOGEN IN PATIENTS WITH TRANSMURAL VS NON-TRANSMURAL INFARCTION

52 patients had transmural and 13 had non-transmural infarction as judged by ECG

Kallikrein inhibitory activity was significantly elevated in the first 24 hours of the disease in the patients with transmural infarction as compared with the non-transmural infarction patients

Maximal plasma prekallikrein decrease takes place at the same time in both infarction groups but is greater in patients with transmural infarction

Maximal plasma kininogen decrease expressed in proportion to serum total protein takes place later in the transmural infarction group than in the non-transmural group It is significantly greater in the transmural group than in the non-transmural group The results are presented in Table IV

Table IV Plasma kallikrein inhibitory activity (IU) on the first day of the disease and maximal plasma prekallikrein decrease (µmoles TAMe/ml of plasma/h) and maximal plasma kininogen decrease (µg Bk/g of serum protein) at the time of their appearance (mean) in transmural and non-transmural infarction patients (means and S.E.M.)

	Transmural (N 52) (time of appearance)	Non-transmural (N 13) (time of appearance)	P
Kallikrein inhibitory activity	1 17 0.044 (24 h)	1.02 0 014 (<24 h)	<0 05
Maximal prekallikrein decrease	37 1 0.38 (60 h)	24 4 1 21 (60 h)	<0.05
Maximal kininogen decrease	15 0 0.13 (40 h)	10.7 0.17 (36 h)	<0.05

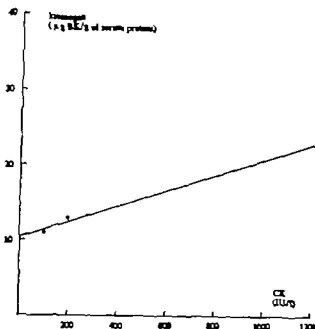


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It can be seen that the activity is highest in the group with mild to moderate hemodynamic disturbances (Group II) and lowest in the most severe group When the value of first 24 hours is compared with other values within each group there is a statistically significant decrease *in the inhibitory activity on the* third to fourth day in Group I (t 1 742 df 43 p<0 05) and in Group II on the third to fourth day (t=2 184 df 58 p<0 05) Within Group III the decrease is never statistically significant

When the three groups are compared with each other it is found that Group I differs significantly from Group II on the second day (t 1 724 *df 48* p<0 05) and after a month (t 1 810 df 38 p<0 05) and *from* Group III *after a week (t 1 762 df 28 p<0 05)*

In Group II the inhibitory activity is significantly higher than in Group III on the second day (t=2 187 df 33 p<0 05) and a week after the onset of the disease (t=2 256 df 34 p<0 05)

Fig 12 shows plasma prekallikrein in hemodynamic subgroups I III

Group I differs from Group II significantly on the *third* to *fourth* day (t 1 751 df 54 p<0 05) and from Group III on the second day (t=2 074 *df 30 p<0 05) the third to fourth day (t 3 327 df 30 p<0 01)* and after a week (t 2 410 df 28 p<0 05) Group II differs significantly from Group III on the third to fourth day (t 1 982 df 36 p<0 05)

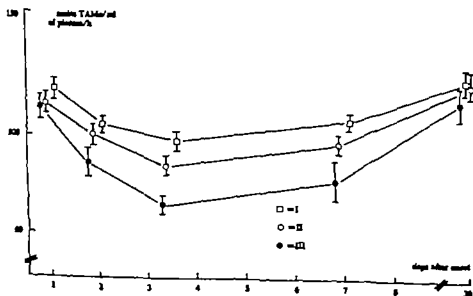


Fig 12 Plasma prekallikrein (means and S E M) in acut my cardi l infarctio g ouped ccordi g t linical hamody amic se erity Group III repres ts the most sever ca es Se to t

DISCUSSION

According to these results changes in the plasma kinin system are greater in transmural than in non-transmural infarctions The results of Dzizinskii and Kuimov (1972) Kedra et al (1973) and Kolber Postepska (1975) did not show this difference It is possible that the greater activation is due to a greater mass of myocardial necrosis

Coronary thrombosis is rare in patients with subendocardial infarction (Roberts and Buja 1972) whereas occlusive thrombosis is more usual in patients with transmural infarction from 54 % (Roberts and Buja 1972) to 95 % (Davies et al 1976)

Changes both in plasma prekallikrein and in kallikrein inhibitory activity are a sensitive indicator of activation of the intrinsic coagulation pathway (Mason and Colman 1971) It is possible that the observed greater changes in transmural infarctions indicate the activation of intrinsic coagulation and subsequent thrombin formation

IV PLASMA KALLIKREIN INHIBITORY ACTIVITY PREKALLIKREIN AND KININOGEN AS RELATED TO CLINICAL HEMODYNAMIC SEVERITY OF AMI

The patients were divided into three subgroups according to clinical hemodynamic criteria Group I had no clinical signs of heart failure the criteria of which are stated in chapter Methods (I 2) There were 25 patients in this group Group II consisted of 33 patients with mild to moderate signs of heart failure and Group III consisted of 7 patients with signs of severe hemodynamic disturbances either of left ventricular failure and/or shock

Kallikrein inhibitory activity in the hemodynamic subgroups is shown in Table V

Tabl V Kallikrei inh b tory activ ty (IU) n acute myocardial infarction grouped according to cli c l hemodynamic severity (means and S E M) Group III represents the most severe cases See text

Group (N)	<24h	24-48h	48-96h	6-8d	30d
I (25)	1 10 ± 0 051	1 03 ± 0 037	1 00 0 025	1 02 ± 0 028	1 07 0 033
II (33)	1 19 0 033	1 11 ± 0 032	1 07 0 044	1 07 ± 0 033	1 16 0 038
III (7)	1 05 ± 0 047	94 ± 0 095	96 0 040	89 ± 0 102	96 0 047

It can be seen that the activity is highest in the group with mild to moderate hemodynamic disturbances (Group II) and lowest in the most severe group When the value of first 24 hours is compared with other values within each group there is a statistically significant decrease in the inhibitory activity on the third to fourth day in Group I (t=1 742 df 43 p<0 05) and in Group II on the third to fourth day (t=2 184 df 58 p<0 05) Within Group III the decrease is never statistically significant

When the three groups are compared with each other it is found that Group I differs significantly from Group II on the second day (t 1 724 df 48, p<0 05) and after a month (t 1 810 df 38 p<0 05) and from Group III after a week (t 1 762 df 28 p<0 05)

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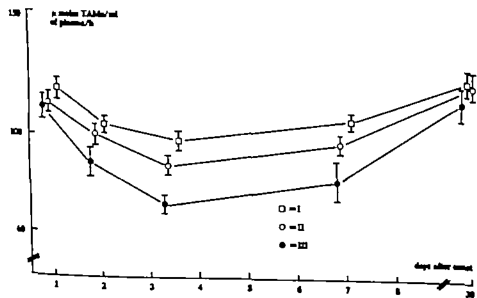


Fig 12 Plasma prekallikrein (means and S E M) in c t myocardial infarctio grouped according to clinic l hemodynamic s erity Gro p III represents the mo t evere cases S ta t

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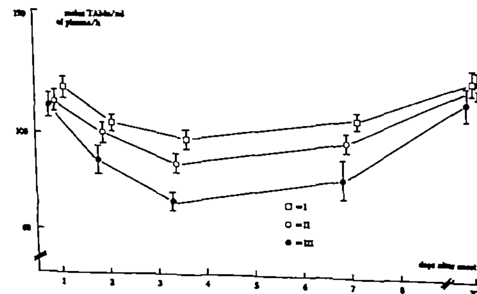


Fig 12 Plasma prekallikrein (means and S E M) in a ut myocardial infarcti n grouped ccording to cli ical hemodynamic ev rity Gro p III repres nts the most sever ases Se te t

As seen in Fig 13 and Fig 14 kininogen drops faster than prekallikrein and reaches the control level sooner When kininogen is expressed as µg of *bradykinin/ml of plasma Group I does not differ significantly from* Group II but with Group III the difference is statistically significant on the second day (t=2 003 df 29 p<0 05) and the third to *fourth day* (t=2 046 df 30 p<0 05) Group II does not differ significantly from Group III

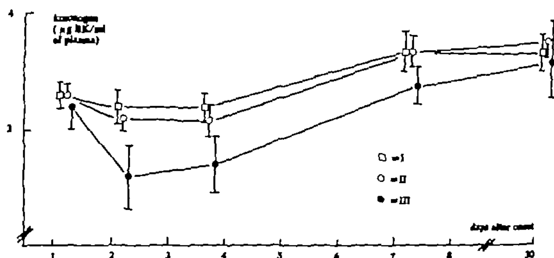


Fig 13 Plasma kininogen (expressed as µg BK/ml of plasma) in acute myocardial infarction grouped according to clinical hemodynamic severity (means and S E M) Group III represents the most severe cases See text

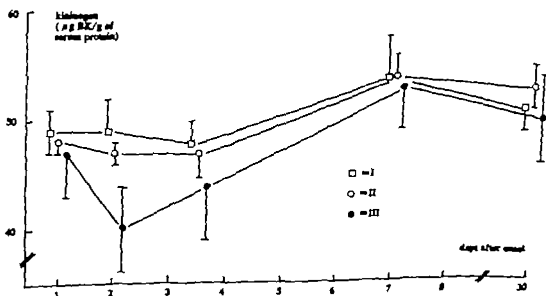


Fig 14 Plasma kininogen expressed as µg 3K/g of serum protein) in acute myocardial infarction grouped according to clinical hemodynamic severity (means and S E M) Group III represents the most severe cases See text

When corrected in proportion to serum protein (µg bradykinin/g of serum protein) there is however a significant difference between Groups II and III on the second day (t 1 376 df 37 p<0 05)

The time of appearance of maximal kininogen level decrease in Group II (mean 39 2 h) is significantly shorter than in Group III (mean 52 3 h) (t 1 738 df 37 p<0 05)

DISCUSSION

Direct hemodynamic measurements were performed only on those patients in this study who were admitted to the intensive care unit However with well documented clinical findings clinical classification by an expert cardiologist leads to the correct conclusion in 80 % of the patients as compared with classification made by direct hemodynamic measurements only (Forrester et al 1977)

Thus the subdivision of the patients was performed by a cardiologist according to clinical records which had been completed bedside by the author in each case 62 % of the patients had at least mild hemodynamic disturbances

Kallikrein inhibitory activity in all subgroups is higher than in the control patients (see Table III) on the first day of the disease with a decline thereafter Kallikrein inhibition is highest in Group II and lowest in Group III It is possible that in the most severe cases this compensatory mechanism collapses In less severe cases it is probably acting normally and most effectively in those patients (Group II) in whom all compensatory mechanisms are expected to be active

The present findings also confirm that both plasma prekallikrein and kininogen consumption is correlated with the hemodynamic severity of acute myocardial infarction The later appearance of maximal kininogen decrease in more severe cases suggests a prolonged activation of the plasma kinin system in these cases

Observations on the association of the hemodynamic severity of infarction ith plasma prekallikrein decrease (Gomazkov 1974 Golikov et al 1977) and with plasma kininogen decrease (Sicuteri et al 1967; Dzizinskii and Kuimov 1972; Ked a et al 1973; Kolber-Postepska 1975) have been made earlier Wiegershausen et al (1967) however noticed no correlation between hemodynamic severity and plasma kininogen consumption

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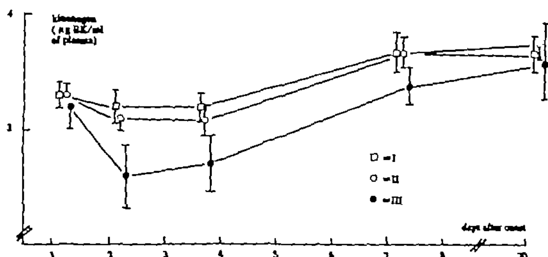


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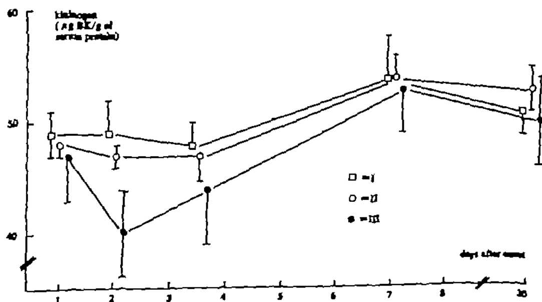


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elevated kallikrein inhibitory activity on the first days after the initial symptoms dyspnea at rest

Pitt et al (1969) assayed the plasma kallikrein system in coronary sinus blood during pacing test in 17 patients Of 11 patients with signs of myocardial ischemia 7 showed activation of the plasma kallikrein system Four patients with pacing-induced angina failed to show activation of the plasma kallikrein system and one of the seven who showed activation of the kallikrein system during myocardial ischemia had only ECG changes but no anginal pain

This along with the present findings suggests that the plasma kallikrein-kinin system alone can hardly be responsible for the pain in myocardial ischemia or infarction

There are no other reports in the literature on the plasma kinin system and on the presence or duration of pain in clinical myocardial ischemia or infarction

Kimura et al (1975) examined the relationship between direct hemodynamic parameters and kininogen and kinin levels in infarction patients They found significant correlations between the lowering of blood pressure total peripheral resistance and increase of circulation time on one hand and plasma kininogen decrease and kinin increase on the other

In the infarction group of the present study there were four patients who died during the stay in hospital Two died of cardiac arrest and two - after being unconscious for a period of time of brain edema Since the group was small and not uniform no attempt was made to draw any conclusions concerning the changes in the plasma kinin system

V PLASMA PREKALLIKREIN AND KININOGEN AS RELATED TO THE DURATION OF PAIN IN ACUTE MYOCARDIAL INFARCTION

The onset of pain was carefully recorded by asking each patient personally and checked from the patient records The duration of pain was estimated using the need of analgesics mostly morphine as an indicator

No attempt was made to evaluate the degree of pain owing to its subjective nature

A direct comparison between each patient s duration of pain and the maximal prekallikrein and kininogen decrease or their time of appearance did not show any correlation

DISCUSSION

The mean duration of pain in the group was 23 8 hours which agrees well with reports by other authors Inoue et al (1977) obtained by asking each patient s complaints of chest pain a mean of 24 hours for the duration of pain in acute myocardial infarction

The findings of this study are not sufficient to show that activation of the plasma kinin system correlates with the presence and/or duration of pain in myocardial infarction

There was only one patient who experienced no pain He had electrocardiographic changes of extensive antero-lateral infarction maximal serum total CK activity of 793 IU/l and severe hemodynamic disturbances This patient showed marked activation of the plasma kinin system a decrease in both prekallikrein and kininogen as well as

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GENERAL DISCUSSION AND CONCLUSIONS

65 patients with acute myocardial infarction admitted to Helsinki University Central Hospital were included in the study Patients over 75 years of age alcoholics and patients who died within two days after admission were excluded Four patients included in the study died during the stay in hospital In other respects the patients represented a typic unselected sample of acute myocardial infarction

16 hospitalized control patients in no way connected with the infarction group were included in order to evaluate the effect of hospitalization and immobilization which appeared not to influence the plasma kallikrein-kinin system

The activation of the plasma kinin system should lead to a decrease in plasma prekallikrein and kininogen with a concomitant rise in plasma kallikrein and bradykinin Simultaneous changes in both plasma kallikrein inhibitory activity and kininase activity are also to be expected Plasma free bradykinin was not measured in this study All the other components of the plasma kinin system mentioned above were determined during the course of acute myocardial infarction i e first second and third or fourth day one week and one month from the onset of the acute symptoms

It was concluded that the plasma kinin system is activated during the acute stage of myocardial infarction This conclusion was based on the observation that both plasma prekallikrein and kininogen decrease Moreover in the very early stage of the disease kallikrein inhibitory activity increases

No changes in spontaneous TAMe-esterase (kallikrein) activity were observed in this study It is however possible that there is an increase in free kallikrein but it either takes place very early during the disease and is thus missed or it is suppressed by the increased kallikrein inhibitory activity It is also possible that changes are not

observed owing to the relative insensitivity of the method The observed decreases in plasma prekallikrein and kininogen agree with earlier observations by others In previous studies no attention has been paid to possible hemodilution or hemoconcentration due to disturbances in the patients fluid balance This possibility along with the observation that serum total protein decreased during the disease led to the expression of plasma kininogen values also in proportion to serum total protein The changes remained significant This is taken as a proof that the decrease is actual and further that it is probably due to kininogen consumption and not to any nonspecific decrease caused by impaired protein synthesis

No changes in kininase activity during myocardial infarction were found The method used measures only the spontaneously occurring kininase activity in plasma It is possible that the marked kininase potential of the lungs for example may easily overcome the kinin splitting activity needed and thus no changes in plasma kininase activity need to occur

In addition to clear signs of the activation of the plasma kinin system in acute myocardial infarction it was found that the magnitude of the changes in plasma prekallikrein and kininogen were in correlation with the severity of the infarction Consequently it was observed that the prekallikrein and kininogen decrease is greater when maximal serum total CK activity is higher and also when the infarction is transmural as compared with the non-transmural infarctions

This suggests that the changes in the plasma kinin system are related to the size of the infarction

The changes in plasma prekallikrein and kininogen were also greater when the clinical hemodynamic situation was more severe Moreover the appearance of maximal kininogen decrease takes place significantly later in more severe cases which indicates longer duration of the activation of the plasma kinin system

Kallikrein inhibitory activity was high on the first day of the disease possibly reflecting an early change in the plasma kinin system In transmural infarctions inhibitory activity was significantly higher than in non-transmural infarctions In hemodynamic subgroup II with mild to moderate hemodynamic disturbances kallikrein inhibitory activity was higher than in the other subgroups

One reason for the interest in the role of the plasma kinin system in ischemic heart disease has been the possibility that the plasma kinins could be the direct cause of ischemic pain

In this study no correlation was found between either the duration or the degree of the acti ation of the plasma kinin system on one hand and the duration of pai on the othe

GENERAL DISCUSSION AND CONCLUSIONS

65 patients with acute myocardial infarction admitted to Helsinki University Central Hospital were included in the study Patients over 75 years of age alcoholics and patients who died within two days after admission were excluded Four patients included in the study died during the stay in hospital In other respects the patients represented a typical unselected sample of acute myocardial infarction

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SUMMARY

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Thus the role of the plasma kinin system as a cause of ischemic pain was not confirmed by the present results It is however possible and indeed likely - that the pain producing action of the kinins in ischemia is a local phenomenon and cannot be detected by measurements of circulating components of the kinin system

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reduction in the course of the disease Plasma kininase activity did not change during the disease and did not differ from that of the control group The severity of the infarction was evaluated by maximal serum total CK activity and by clinical hemodynamic criteria as well as by dividing the patients into transmural and non transmural infarction groups according to ECG criteria There was a significant correlation between the plasma prekallikrein and kininogen decrease and the maximal serum total CK activity The patients were divided into three subgroups according to clinical hemodynamic criteria In the first group there were no signs of hemodynamic disturbances In the second group there were mild to moderate signs of hemodynamic disturbances and in the third group the disturbances were severe It was found that the decrease in plasma prekallikrein and kininogen is greatest in the third group and smallest in the first group Moreover the time of appearance of the maximal decrease in plasma kininogen took place significantly later in the third group than in the second group Plasma kallikrein inhibitory activity was highest in the second group and lowest in the third group Plasma prekallikrein and kininogen decrease was significantly greater and plasma kallikrein inhibitory activity significantly higher in the group with transmural infarction than in the group with non transmural infarction No correlation was found between the duration of pain and the magnitude and the time of appearance of the maximal decrease in plasma prekallikrein and kininogen

On the basis of this study it is concluded that the plasma kinin system is activated in the course of acute myocardial infarction and that the magnitude of the changes in the components of the plasma kinin system is correlated with the extent and clinical severity of the infarction but not with the presence or duration of pain

Colman R.W Formation of human plasma kinin N Engl J Med 291 509 1974

Colman R W Bagdasarian A Talamo R C Seavey M Scott C F Kaplan A P Williams trait Combined deficiency of plasma plasminogen proactivator kininogen and a new progoagulant factor Fed Proc 34 859 1975 (abstr)

Colman R W Girey G J D Zacest R Talamo R C The human plasma kallikrein-kinin system Prog Hematol 7 255 1971

Colman R W Mason J W Sherry S The kallikreinogen kallikrein enzyme system of human plasma Assay of components and observations in disease states Ann Intern Med 71 763 1969

Colman R W Mattler L Sherry S : Studies on the prekallikrein (kallikreinogen) kallikrein enzyme system of human plasma II Evidence relating the kaolin activated arginine esterase to plasma kallikrein J Clin Invest 48 23 1969 (b)

Davies M J Woolf N Robertson W B Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi Brit. Heart J 38. 659 1976

Diaz P E Fishbein H C Davis M A Askenazi J Maroko P R Effect of the kallikrein inhibitor Aprotinin on myocardial ischemic injury after coronary occlusion in the dog Am J Cardiol 40 .41 1977

Diniz C R Carvalho I F A micromethod for determination of brady kininogen under several conditions Ann N Y Acad Sci 104 77 1963

Diniz C R Carvalho I F Ryan J Rocha e Silva M A micromethod for the determination of bradykininogen in blood plasma Nature 192 1194 1961

Donaldson V H Evans R R A biochemical abnormality in hereditary angioneurotic edema Absence of serum inhibitor of C 1 esterase Am J Med 35 35 1963

Dzizinskii A A Kuimov A D Blood kinin system in pathogenesis and clinic of ischaemic heart disease Cor Vasa 14 (1) 9 1972

Edery H Lewis G P Inhibition of plasma kininase activity at slightly acid pH Brit J Pharmacol 19: 299 1962

Eisen V Effect of hexadimethrine bromide on plasma kinin formation hydrolysis of p-tosyl-L arginine methyl ester and fibrinolysis Brit J Pharmacol 22 87 1964

Eisen V Enzymic aspects of plasma kinin formation Proc Roy Soc B 173 351 1969

Eisen V Vogt W : Plasma kininogenases and their activators In E G Erdos (ed) Handbook of experimental Pharmacology XXV 82 Springer Verlag Berlin-Heidelberg-New York 1970

Elliott D.F Lewis G P Horton E W The structure of bradykinin a plasma kinin from ox blood Biochem. Biophys Res Commun 3 87 1960

Elliot A H Nuzum, F R : The urinary excretion of a depressor substance (Kallikrein of Frey and Kraut) in arterial hypertension Endocrinology 18 462 1934

REFERENCES

Aarsen P N Sensitization of guinea pig ileum to the action of bradykinin by trypsin hydrolysate of ox and rabbit plasma Brit J Pharmacol 32 453 1968

Armstrong D A J Chemical excitants of cutaneous pain University of London Thesis 1957

Assali N S Johnson G H Brinkman C R Huntsman D J Effects of bradykinin on the fetal circulation Am J Physiol 221 1375 1971

Barrett A J Starkey P M The interaction of alpha 2-macroglobulin with proteinases Biochem J 133 709 1973

Beloff A Peters R A Observations upon thermal burns The influence of moderate temperature burns upon a proteinase of skin J Physiol (London) 103 461 1945

Blomquist H Hamberg U Kininogen level in clinical pancreatitis during treatment with trypsin inhibitor from bovine lung Scand J Clin Lab Invest 24 (Suppl 107) 173 1969

Boissonnas R A Guttmann S Jaquenoud P A Konzett H Stürmer E Synthesis and biological activity of peptides related to bradykinin Experientia 16 326 1960

Brecher G A Brobmann G F Effect of kallikrein on the cardiovascular system In E G Erdös (ed) Handbook of experimental Pharmacology XXV 351 Springer-Verlag Berlin Heidelberg-New York 1970

Burch G E DePasquale N P Bradykinin digital blood flow and the arteriovenous anastomoses Circ Res 10 105 1962

Campbell A G M Dawes G S Fishman A P Hyman A I Perks A M The release of a bradykinin like pulmonary vasodilator substance in foetal and new-born lambs J Physiol (London) 159 83 1968

Castania A Rotschild A M Lowering of kininogen in rat blood by adrenaline and its inhibition by sympatholytic agents heparin and aspirin Br J Pharmacol 50 375 1974

Collier H O J Self antagonism of bronchoconstriction induced by bradykinin and angiotensin In E G Erdös N Back F Sicuteri (eds) Hypotensive peptides 305 Springer Verlag Berlin Heidelberg New York 1966

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Colman R W Mattler L Sherry S Studies on the prekallikrein (kallikreinogen) kallikrein enzyme system of human plasma II Evidence relating the kaolin activated arginine esterase to plasma kallikrein J Clin Invest 48 23 1969 (b)

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Eisen V : Enzymic aspects *of plasma kinin formation Proc Roy Soc B* 173: 351 1969

Eisen V Vogt W Plasma kininogenases and their activators In E G Erdos (ed) Handbook of experimental Pharmacology XXV 82 Springer Verlag Berlin-Heidelberg-New York 1970

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Castania A Rotschild A M Lowering of kininogen in rat blood by adrenaline and its inhibition by sympatholytic agents heparin and aspirin Br J Pharmacol 50 375 1974

Collier H O J Self antagonism of bronchoconstriction induced by bradykinin and angiotensin In E G Erdös M Back F Sicuteri (eds) Hypotensive peptides 305 Springer-Verlag Berlin-Heidelberg New York 1966

Haberland G L Proteases in myocardial infarction In H. Cantin G.L Haberland G Schnells H Selye (eds) New aspects of Trasylol therapy 8 19 Schattauer-Verlag Stuttgart-New York 1975

Habermann E Kininogens In E G Erdös (ed) *Handbook of experimental Pharmacology XXV* 250 Springer Verlag Berlin-Heidelberg-New York 1970

Habermann E Blennemann G *Über Substrate und Reaktionsprodukte der* kininbildenden Enzyme Trypsin Serum- und Pankreas kallikrein sowie vom *crotalusgift Arch exp* Path Pharmak 249 357 1964

Haddy F J Emerson Jr T E Scott J B Daugherty Jr R M The effects of the kinins on the cardiovascular system In E G Erdös (ed) Handbook *of experimental* Pharmacology XXV 363 Springer Verlag Berlin-Heidelberg-New York 1970

Hamberg U Isolation of bradykinin from human plasma Ann Acad Sci Fenn Ser A II Chemica 113 1 1962

Hamberg U Plasma protease and kinin release with special reference to plasmin Ann N Y Acad Sci 146 517 1968

Hamberg *U Kininogen in human plasma after fibrinolytic activation* Scand J Clin Lab Invest 24 (Suppl 107) 37 1969

Hamberg U Tallberg Th Preparation of monospecific antiserum to *human LMW kininogen using immunoadsorbents J Immunol Methods 2* 17 1972

Hamberg U Elg P Nissinen E Stelwagen P Purification and heterogeneity of human kininogen Int J Peptide Protein Res *7:* 261 1975

Harpel P C Human plasma alpha 2-macroglobulin An inhibitor of plasma kallikrein J Exp Med 132 329 1970

Harpel P C Circulating inhibitors of human plasma kallikrein In: J J *Pisano and K F Austen (eds) Chemistry and Biology of the* Kallikrein-Kinin System in Health and Disease Fogarty International Center Proceedings 27 169 U S Government Printing Office Washington D C 1976

Hashimoto, K. Hirose M. Furukawa S Hayakawa H Kimura E Changes in hemodynamics and bradykinin concentration in coronary sinus blood in experimental coronary artery occlusion Jap Heart J 18 679 1977

Herxheimer A. Schachter M Wheal and flare in human skin produced by histamine and other substances J *Physiol (London) 145 34p 1959*

Hilton S M. Lewis G P The mechanism of the functional hyperaemia *in* the submandibular salivary gland J Physiol (London) 128. 235 1955

Hilton S M. Lewis G P The relationship between glandular activity bradykinin *formation* and functional vasodilatation in the sub-mandibular salivary gland J Physiol (London) 134 471 1956

Holdstock D J Mathias A P Schachter M A comparative study of kinin kallidin and bradykinin Brit J Pharmacol 12 149 1957

Erdös E G Enzymes that inactivate active polypeptides Biochem Pharmacol 8 112 1961

Erdös E G The kinins A status report Biochem Pharmacol 25 1563 1976

Erdös E G Sloane E M An enzyme in human plasma that inactivates bradykinin and kallidins Biochem Pharmacol 11 585 1962

Feldberg W Lewis G P Action of peptides on adrenal medulla release of adrenalin by bradykinin and angiotensin J Physiol (London) 171 98 1964

Ferreira S H Contribution of prostaglandins to the inflammatory signs and symptoms Biochem Soc Trans 2 1189 1974

Ferreira S H Vane J R The disappearance of bradykinin and eledoisin in the circulation and vascular beds of the cat Brit J Pharmacol 30 417 1967

Forrester, J S Diamond G A Swan H J C Correlative classification of clinical and hemodynamic function after acute myocardial infarction Am J Cardiol 39 137 1977

Fox R H Hilton S M Bradykinin formation in human skin as a factor in heat vasodilatation J Physiol (London) 142 219 1958

Frey E K Zusammenhänge zwischen Herzarbeit und Nierentätigkeit Arch klin Chir 142 663 1926

Frey E K Kraut H Ein neues Kreislaufhormon und seine Wirkung Arch exp Path Pharmak 133 1 1928

Frey E K Kraut H Werle E Kallikrein Padutin Stuttgart Enke 1950

Furukawa S Hashimoto K Hayakawa H Ushiyama S Kimura E Miynaga Y Kimura Y Changes in bradykininogen bradykinin and bradykininase after experimental artery ligation Jap Circ J 33 886 1969

Furuyama T Suzuki C Saito H Onozawa Y Shioji R Rikumaru S Abe K Yoshinaga K Effect of bradykinin and eledoisin on renal function in the dog Tohoku J Exp Med 89 69 1966

Golikov A P Bobkov A I Ivleva V I Changes in sympatho-adrenal and kallikrein kinin systems in the terminal stage of extensive myocardial infarction Cor Vasa 19(3) 169 1977

Gomazkov O A Das Kallikrein Kinin System bei Myokard ischämie und Herz infarkt - Experimentelle Untersuchungen Med Welt 25 804 1974

Greenwood F C Hunter W H Glower J S The preparation of ^{131}I labelled human growth hormone of high specific radioactivity Biochem J 89 114 1963

Guzman F Braun C Lim R K S Visceral pain and the pseudoaffective response to intra arterial injection of bradykinin and other algesic agents Arch Int Pharmacodyn 136 353 1962

Haanen C Morselt G Some observations on the role of Hageman factor in blood coagulation Thromb Diath Haemorrh 6 261 1961

Kraut H Frey E K. Bauer E Über ein neues Kreislaufhormon II Z physiol Chem 175 97 1928

Kraut, H Frey E K Werle E Der Nachweis eines Kreislaufhormones in der Pankreasdrüse Z physiol Chem 189 97 1930

Kraut, H Frey E K. Werle E Über den Nachweis und das Vorkommen des Kallikreins im Blut VIII mitt Über Kallikrein Z physiol Chem 222 73 1933

Landerman N S Webster M E Becker E L Ratcliffe H D Hereditary angioneurotic edema I Deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein J Allerg 33 330 1952

Lautsberg L A. Nekrasova A A. Tspkova N K Changes in blood kinin system in various physiological states Cor Vasa 15 (3) 190, 1973

Lewis G P Bradykinin biochemistry pharmacology and its physiological role in controlling local blood flow Sci Basis Med 14: 242 1962

Lewis G P The role of plasma kinins as mediators of functional vaso-dilatation Gastroenterology 52 406 1967

Lewis T Pickering G W Rotschild P Observations upon muscular pain in intermittent claudication Heart 15: 359 1929-1931

Louhija A Sipilä R : Plasma kininogen determination by use of crude and purified trypsin hydrolysates Acta Pharmacol Toxicol 30 122 1971

Louhija A. Sipilä R The presence of a smooth muscle contracting and bradykinin potentiating factor in plasma Biochem Pharmacol 21 1151 1972

Malofiejew M. The plasma kinin forming system in labour Clin Sci Mol Med 45 429 1973

Margolis J Activation of plasma by contact with glass Evidence for a common reaction which releases plasma kinin and initiates coagulation J Physiol (London) 144 1 1958

Margolis J : The interrelationship of coagulation of plasma and release of peptides Ann N Y Acad Sci 104 133 1963

Margolius H S Pisano J J Geller R G Sjoerdsma A Altered urinary kallikrein excretion in human hypertension Lancet 2 1063 1971

Mashford M.L Roberts M L Radioimmunoassay of circulating blood kinin levels In: N Back F Sicuteri (eds) Vasopeptides Chemistry Pharmacology and Pathophysiology Adv Exp Med Biol 21 23 Plenum Press New York London 1972

Mason D T Melmon K.L Effects of bradykinin on forearm venous tone and vascular resistance in man Circ Res 17 106 1965

Mason J W Colman R W : The role of Hageman factor in disseminated intravascular coagulation by septicemia neoplasia or liver disease Throm Diath Haemorrh 26 325 1971

Massion W H Blumel G Peschl L : The role of proteolytic enzymes in refractory hypertension In: W Brendel G L Haberland (eds): New aspects of Trasylol the apy 5 73 Schattauer-Verlag Stuttgart-New York 1971

Horton E W The role of bradykinin in the peripheral nervous system Ann N Y Acad Sci 104 250 1963

Inoue M Hori M Fukui S Abe H Minamino T Kodama K Oghitani M Evaluation of evolution of myocardial infarction by serial determinations of serum creatine kinase Brit Heart J 39 485 1977

Jacobsen S Kriz M Some data on two purified kininogens from human plasma Brit J Pharmacol 29 25 1967

Kagen L J Becker E L Inhibition of permeability globulins by C 1 esterase inhibitor Fed Proc 22 613 1963

Kaplan A P Austen K F Prealbumin activator of prekallikrein II Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin J Exp Med 133 696 1971

Kaplan A P Meier H D Yecies L D Heck L W Hageman factor and its substrates The role of Factor XI Prekallikrein and Plasminogen proactivator in coagulation fibrinolysis and kinin generation In J J Pisano and K F Austen (eds) Chemistry and Biology of the Kallikrein-Kinin System in Health and Disease Fogarty International Center Proceedings 27 237 U S Government Printing Office Washington D C 1976

Kedra M Kleinrok Z Kolber Postepska B Szurska G Plasma kininogen in patients with myocardial infarction Cor Vasa 15 (1) 1 1973

Keele C A Armstrong D Substances producing pain and itch Edward Arnold Ltd London 1965

Kellermayer R W Breckenridge R T The inflammatory process in acute gouty arthritis I Activation of Hageman factor by sodium urate crystals J Lab Clin Med 65 307 1965

Kimura E Hashimoto K Furukawa S Hayakawa H Changes in bradykinin level in coronary sinus blood after the experimental occlusion of a coronary artery Am Heart J 85 635 1973

Kimura E Hashimoto K Hamamoto H Changes in kinin system and hemodynamics in acute stage of clinical myocardial infarction In M Cantin G L Haberland G Schnells H Selye (eds) New aspects of Trasylol therapy 8 393 Schattauer Verlag Stuttgart-New York 1975

Klein M S Shell W E Sobel B E Serum creatine phosphokinase isoenzymes after intramuscular injections surgery and myocardial infarction Cardiovasc Res 7 412 1973

Kolber-Postepska B Changes in the plasma kinin system in patients with myocardial infarction Cor Vasa 17 (3) 169 1975

Konttinen A Hupli V Louhija A Härtel G Origin of elevated serum enzyme activities after direct current counter shock N Engl J Med 281 231 1969

Konttinen A Somer H Specificity of serum creatine kinase enzymes in diagnosis of acute myocardial infarction Brit Med J 1 386 1973

Konzett H Stürmer E Biological activity of synthetic polypeptides with bradykinin like properties Brit J Pharmacol 15 544 1960

Oates J A. Melmon K.L Sjoerdsma A Gillespie L Mason D T Release of a kinin peptide in the carcinoid syndrome Lancet 1 514 1964

Ogston, D Ogston C M. Ratnoff O D Studies on the clot promoting effect of skin J Lab Clin Med 73 70 1969

Peltola P Release of serotonin in man induced by some polypeptides Adv Exp Med Biol 21 483 1972

Pierce J W Webster M E. Human plasma kallidins Isolation and chemical studies Biochem Biophys Res Commun 5 353 1961

Pierce J V Webster M E The purification and some properties of two different kallidinogens from human plasma In E G Erdös M Back F Sicuteri (eds) Hypotensive peptides 130 Springer-Verlag New York 1966

Pitt B Mason J Conti C R. Colman R.W Activation of the plasma kallikrein system during myocardial ischemia Adv Exp Med Biol 8 403 1970

Ratnoff O D Some recent advances in the study of hemostasis Circ Res 35. 1 1974

Ratnoff O D Colopy J E A familial hemorrhagic trait associated with a deficiency of a clot promoting fraction in plasma J Clin Invest 34 602 1955

Reichgott M J Melmon K L Bradykinin and the cardiovascular system Circulation 42 563 1970

Roberts W C Buja L M The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction A study of 107 necropsy patients Am J Med 52 425 1972

Rocha e Silva M. Antonio A Release of bradykinin and the mechanism of production of a thermic edema (45°C) in the rat paw Med Exp (Basel) 3. 371 1960

Rocha e Silva M. Beraldo W T Rosenfeld G Bradykinin a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin Am J Physiol 156 261 1949

Rocha e Silva M Rosenthal S R Release of pharmacologically active substances from the rat skin in vivo following thermal injury J Pharmacol Exp Ther 132 110 1961

Rowley D A. Venous constriction as cause of increased vascular permeability produced by 5-hydroxytryptamine histamine bradykinin and 48/80 in rat. Brit J Exp Path 45 56 1964

Saameli K. Estes T K.A.B Bradykinin and cardiovascular system: Estimation of half life Am J Physiol 203 261 1962

Schachter M Kallikreins and kinins Physiol Rev 49 509 1969

Sicuteri F Bradykinin and intracranial circulation in man In E G Erdos (ed) Handbook of experimental Pharmacology XXV 482 Springer-Ve lag Berlin-Heidelberg-New York 1970

Sicuteri F : Summary of literature published in Italian In E G Erdos (ed) Handbook of experimental Pharmacology XXV 610 Springer-Verlag Be lin-Heidelberg-New York 1970 (b)

Mathey D Biefield W Hanrath P Effert S Attempt to quantitative relation between cardiac function and infarct size in acute myocardial infarction Brit Heart J 36 271 1974

McConnel D J Inhibitors of kallikrein in human plasma J Clin Invest 51 1611 1972

McGiff J C Nasjletti A Kinins renal function and blood pressure regulation Fed Proc 35 172 1976

McGiff J C Terragno N A Malik K U Lonigro A J Release of a prostaglandin E-like substance from canine kidney by bradykinin comparison with eledoisin Circ Res 31 36 1972

Melmon K L Cline M J Kinins Am J Med 43 153 1967

Melmon K L Cline M J Hughes T Nies A S Kinins possible mediators of neonatal circulatory changes in man J Clin Invest 47 1295 1968

Melmon K L Webster M E Goldfinger S E Seegmiller J E The presence of a kinin in inflammatory synovial effusion from arthritides of varying etiologies Arthr and Rheum 10 13 1967

Meltzer H Y Mrozak S Boyer M Effects of intramuscular injections on serum creatine phosphokinase activity Am J Med Sci 259 42 1970

Mersey J H Williams N K Hollenberg N K Dluhy R G Relationship between aldosterone and bradykinin Circ Res 40 (Suppl I) 84 1977

Montague D Rosas R Bohr D F Bradykinin vascular relaxant cardiac stimulant Science 141 907 1963

Moskowitz R W Schwartz H J Michel B Ratnoff O D Astrup T Generation of kinin like agents by chondroidin sulfate heparin chitin sulfate and human articular cartilage Possible patho physiologic implications J Lab Clin Med 76 790 1970

Movat H Z DiLorenzo N L Activation of the plasma kinin system by antigen antibody aggregates I Generation of permeability factor in guinea pig serum Lab Invest 19 187 1968

Nasjletti A Colina-Churio J McGiff J C Disappearance of bradykinin in the renal circulation of dogs Effects of kininase inhibition Circ Res 37 59 1975

Needleman P Key S L Denny S E Isakson P C Marshall G R Mechanism and modification of bradykinin induced coronary vasodilation Proc Nat Acad Sci U S A 72 2060 1975

Niewiarowski S Bănkowski E Rogowicka I Studies on the adsorption and activation of the Hageman factor (factor XII) by collagen and elastin Thromb Diath Haemorrh 14 387 1965

Nossel H L Activation of factors XII (Hageman) and XI (PTA) by skin contact Proc Soc Exp Biol Med 122 16 1966

Nustad K Relationship between kidney and urinary kininogenase Brit J Pharmacol 39 73 1970

Nydick I Wroblewski F LaDue J Evidence for increased serum glutamic oxalacetic transaminase (S-GOT) activity following graded myocardial infarcts in dogs Circulation 12 161 1955

Oates J A. Melmon K.L Sjoerdsma A. Gillespie L Mason D T Release of a kinin peptide in the carcinoid syndrome Lancet 1 514 1964

Ogston D Ogston C M. Ratnoff O D Studies on the clot promoting effect of skin J Lab Clin Med 73 70 1969

Peltola P Release of serotonin in man induced by some polypeptides Adv Exp Med Biol 21 483 1972

Pierce J V Webster M E. Human plasma kallidins Isolation and chemical studies Biochem Biophys Res Commun 5 353 1961

Pierce J V Webster M E The purification and some properties of two different kallidinogens from human plasma In E G Erdös N Back F Sicuteri (eds) Hypotensive peptides 130 Springer-Verlag New York 1966

Pitt, B Mason J Conti C R. Colman R.W Activation of the plasma kallikrein system during myocardial ischemia Adv Exp Med Biol 8 403 1970

Ratnoff O D Some recent advances in the study of hemostasis Circ. Res 35 1 1974

Ratnoff O D Colopy J E : A familial hemorrhagic trait associated with a deficiency of a clot-promoting fraction in plasma J Clin Invest 34 602 1955

Reichgott M.J Melmon K L Bradykinin and the cardiovascular system Circulation 42 563 1970

Roberts W C , Buja L M : The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction A study of 107 necropsy patients Am J Med 52 425 1972

Rocha e Silva M. Antonio A Release of bradykinin and the mechanism of production of a thermic edema (45°C) in the rat paw Med Exp (Basel) 3 371 1960

Rocha e Silva M. Beraldo W T Rosenfeld G. Bradykinin a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin Am. J Physiol 156 261 1949

Rocha e Silva M. Rosenthal S R Release of pharmacologically active substances from the rat skin in vivo following thermal injury J Pharmacol Exp Ther 132: 110 1961

Rowley D A. Venous constriction as cause of increased vascular permeability produced by 5-hydroxytryptamine histamine bradykinin and 48/80 in rat Brit J Exp Path 45 56 1964

Saameli K Eskes T K.A.B Bradykinin and cardiovascular system. Estimation of half life Am J Physiol 203 261 1962

Schachter M. Kallikreins and kinins Physiol Rev 49: 509 1969

Sicuteri F Bradykinin and intracranial circulation in man In E G Erdös (ed) Handbook of experimental Pharmacology XXV 482 Springer-Verlag Berlin-Heidelberg-New York 1970

Sicuteri F : Summary of literature published in Italian

Mathey D Biefield W Hanrath P Effert S Attempt to quantitative relation between cardiac function and infarct size in acute myocardial infarction Brit Heart J 36 271 1974

McConnel D J Inhibitors of kallikrein in human plasma J Clin Invest 51 1611 1972

McGiff J C Nasjletti A Kinins renal function and blood pressure regulation Fed Proc 35 172 1976

McGiff J C Terragno N A Malik K U Lonigro A J Release of a prostaglandin E-like substance from canine kidney by bradykinin comparison with eledoisin Circ Res 31 36 1972

Melmon K L Cline M J Kinins Am J Med 43 153 1967

Melmon K L Cline M J Hughes T Nies A S Kinins possible mediators of neonatal circulatory changes in man J Clin Invest 47 1295 1968

Melmon K L Webster M E Goldfinger S E Seegmiller J E The presence of a kinin in inflammatory synovial effusion from arthritides of varying etiologies Arthr and Rheum 10 13 1967

Meltzer H Y Mrozak, S Boyer M Effects of intramuscular injections on serum creatine phosphokinase activity Am J Med Sci 259 42 1970

Mersey J H Williams N K Hollenberg N K Dluhy R G Relationship between aldosterone and bradykinin Circ Res 40 (Suppl I) 84 1977

Montague D Rosas R Bohr D F Bradykinin vascular relaxant cardiac stimulant Science 141 907 1963

Moskowitz R W Schwartz H J Michel B Ratnoff O D Astrup T Generation of kinin like agents by chondroidin sulfate heparin chitin sulfate and human articular cartilage Possible pathophysiologic implications J Lab Clin Med 76 790 1970

Movat H Z DiLorenzo N L Activation of the plasma kinin system by antigen antibody aggregates I Generation of permeability factor in guinea pig serum Lab Invest 19 187 1968

Nasjletti A Colina-Churio J McGiff J C Disappearance of bradykinin in the renal circulation of dogs Effects of kininase inhibition Circ Res 37 59 1975

Needleman P Key S L Denny S E Isakson P C Marshall G R Mechanism and modification of bradykinin induced coronary vasodilation Proc Nat Acad Sci U S A 72 2060 1975

Niewiarowski S Bánkowski E Rogowicka I Studies on the adsorption and activation of the Hageman factor (factor XII) by collagen and elastin Thromb Diath Haemorrh 14 387 1965

Nossel H L Activation of factors XII (Hageman) and XI (PTA) by skin contact Proc Soc Exp Biol Med 122 16 1966

Nustad K Relationship between kidney and urinary kininogenase Brit J Pharmacol 39 73 1970

Nydick I Wroblewski F LaDue J Evidence for increased serum glutamic oxalacetic transaminase (S-GOT) activity following graded myocardial infarcts in dogs Circulation 12 161 1955

Vogel R Zickgraf Rüdel G Evaluation of the role of kinins in pathological and clinical conditions the therapeutic use of kallikrein inhibitor In: E G Erdös (ed) Handbook of experimental Pharmacology XXV 550 Springer-Verlag Berlin Heidelberg-New York 1970

Waldmann R Abraham J P Fitzgerald factor A heretofore unrecognized coagulation factor Blood 44 934 1974 (abstr)

Walsh P Role of platelets in the contact phase of blood coagulation Brit J Haematol 22 237 1972

Webster M E Gilmore J P Influence of kallidin-10 on renal function Am J Physiol 206 714 1964

Webster M.E Maling H M Evidence for and against the kinins as endogenous mediators of arthritis Adv exp Med Biol 8 493 1970

Webster M E Pierce J W Action of the kallikreins on synthetic ester substrates Proc Soc Exp Biol Med 107 186 1961

Webster M.E Pierce J W : The nature of the kallidins released from human plasma by kallikreins and other enzymes Ann N Y Acad Sci 104 91 1963

Webster M E Ratnoff O D Role of Hageman factor in the activation of vasodilator activity in human plasma Nature 192 180 1961

Weichselbaum, T E : Accurate and rapid method for determination of proteins in small amounts of blood serum and plasma Am J clin Path 7: 40 1946

Weiss A S Gallin J I Kaplan A P Fletcher factor deficiency A diminished rate of Hageman factor activation caused by absence of prekallikrein with abnormalities of coagulation fibrinolysis chemotactic activity and kinin generation J Clin Invest 53 622 1974

Werle E Über die Inaktivierung des Kallikreins II Mitt Biochem Z 273 291 1934

Werle E Berek U Zur Kenntnis des Kallikreins Angew Chem 60 A 53 1948

Werle E Berek U Über Kallidin Biochem Z 320 136 1950

Werle E Forell M M Meier L Zu Kenntnis der blutdrucksenkenden Wirkung des Trypsins Arch exp Path Pharmak 225 369 1955

Werle E Götze W Keppler E Über die Wirkung des Kallikreins auf den isolierten Darm und über eine neue darmkontrahierende Substanz Biochem Z 289 217 1937

Werle E von Roden P Über das Vorkommen von Kallikrein in den Speicheldrüsen und im Hundspeichel Biochem Z 286 213 1936

Wiegershausen B Henninghausen G Klausch B Körber H G Hauteur F Der Plasmakininogenspiegel und die Glutamat-Oxalazetat Transaminase-Aktivität nach Myokardinfa kt (Analyse bei 24 Patienten) Dtsch Gesh W 23 1785 1968

Wilkens H J Steger R Back N Effect of protease inhibitor Trasylol in acute coronary occlusion in dogs In M Cantin G L Haberland G Schoells H Selye (eds) New aspects of Trasylol therapy 8: 381 Schattauer-Verlag Stuttgart New York 1975

Sicuteri F Antonini F M DelBianco P L Franchi G Curradi C Pre kallikrein and kallikrein inhibitor in plasma of patients affected by recent myocardial infarction Adv Exp Med Biol 21 445 1972

Sicuteri F DelBianco P L Curradi C Monetti G The kinin system in cardiogenic shock In M Cantin G L Haberland G Schnells H Selye (eds) New aspects of Trasylol therapy 8 357 Schattauer-Verlag Stuttgart New York 1975

Sicuteri F Franchi G DelBianco P L DelBene E A contribution to the interpretation of shock and pain in myocardial infarction Malattie Cardiovasc 8 343 1967

Siegelman A M Carlsen A S Robertson T Investigation of serum trypsin and related substances I The quantitative demonstration of trypsin like activity in human blood serum by a micromethod Arch Biochem 97 159 1962

Sipilä R The plasma kinin system in acute pancreatitis Dissertation Helsinki 1977

Sipilä R Louhija A The application of bradykinin radioimmunoassay to plasma kininogen determination Biochem Pharmacol 25 543 1976

Sobel B E Bresnahan G F Shell W E Yoder R D Estimation of infarct size in man and its relation to prognosis Circulation 46 640 1972

Somer H Konttinen A Demonstration of creatine kinase isoenzymes by fluorescence technique Clin Chim Acta 40 133 1972

Staszewska Barczack J Ferreira S H Vane J R An excitatory nociseptive cardiac reflex elicted by bradykinin and potentiated by prostaglandins and myocardial ischemia Cardiovasc Res 10 314 1976

Staszewska Barczack J Vane J R The release of catecholamines from the adrenal medulla by peptides Brit J Pharmacol 30 655 1967

Streeten D H P Kerr L P Kerr C B Prior J C Dalakos T G Hyperbradykininism A new orthostatic syndrome Lancet 2 1048 1972

Talamo R C Haber E Austen K F A radioimmunoassay for bradykinin in plasma and synovial fluid J Lab Clin Med 74 816 1969

Terragno D A Crowshaw K Terragno N A McGiff J G Prostaglandin synthesis by bovine mesenteric arteries and veins Circ Res 36 37 (Suppl I) 1 1975

Trautschold I Assay methods in the kinin system In E G Erdös (ed) Handbook of experimental Pharmacology XXV 52 Springer Verlag Berlin Heidelberg New York 1970

Uchida Y Kamisaka K Ueda H Developmental mechanism of anginal pain excitation dynamics of the cardiac sympathetic afferent nerve Jap Circ J 35 147 1971

Uchida Y Murao S Bradykinin induced excitation of afferent sympathetic nerve fibers Jap Heart J 15 84 1974

Uchida Y Ueda H Kininogen and kinin activity during local ischaemia in man Jap Heart J 10 503 1969

Ungar G Release of proteolytic enzyme in anaphylactic and peptone shock in vitro Lancet 1 708 1947

Vogel R Zickgraf Rüdel G Evaluation of the role of kinins in pathological and clinical conditions the therapeutic use of kallikrein inhibitor In E G Erdös (ed) Handbook of experimental Pharmacology XXV 650 Springer Verlag Berlin-Heidelberg-New York 1970

Waldmann R Abraham J P Fitzgerald factor A heretofore unrecognized coagulation factor Blood 44 934 1974 (abstr)

Walsh P Role of platelets in the contact phase of blood coagulation Brit. J Haematol 22 237 1972

Webster M E Gilmore J P Influence of kallidin-10 on renal function Am. J Physiol 206 714 1964

Webster M E Maling H M Evidence for and against the kinins as endogenous mediators of arthritis Adv exp Med Biol 8 493 1970

Webster M E Pierce J W Action of the kallikreins on synthetic ester substrates Proc Soc Exp Biol Med 107 186 1961

Webster M E Pierce J W The nature of the kallidins released from human plasma by kallikreins and other enzymes Ann N Y Acad Sci 104 91 1963

Webster M E Ratnoff O D Role of Hageman factor in the activation of vasodilator activity in human plasma Nature 192 180 1961

Weichselbaum T E Accurate and rapid method for determination of proteins in small amounts of blood serum and plasma Am J clin Path 7 40 1946

Weiss A.S Gallin J I Kaplan A P Fletcher factor deficiency A diminished rate of Hageman factor activation caused by absence of prekallikrein with abnormalities of coagulation fibrinolysis chemotactic activity and kinin generation J Clin Invest 53 622 1974

Werle E Über die Inaktivierung des Kallikreins II Mitt Biochem Z 273 291 1934

Werle E Berek U Zur Kenntnis des Kallikreins Angew Chem 60 A 53 1948

Werle E Berek U Über Kallidin Biochem Z 320 136 1950

Werle E Forell M M Meier L Zur Kenntnis der blutdrucksenkenden Wirkung des Trypsins Arch exp Path Pharmak 225 369 1955

Werle E Götze W Keppler E Über die Wirkung des Kallikreins auf den isolierten Darm und über eine neue darmkontrahierende Substanz Biochem Z 289 217 1937

Werle E. von Roden P Über das Vorkommen von Kallikrein in den Speicheldrüsen und im Mundspeichel Biochem Z 286 213 1936

Wiegershausen B Henninghausen G Klausch B Körber H G Hauzeur F : Der Plasmakininogenspiegel und die Glutamat-Oxalazetat Transaminase-Aktivitat nach Myokardinfarkt (Analyse bei 24 Patienten) Dtsch Gesh W 23: 1785 1968

Wilkens H J Steger R Back N : Effect of protease inhibitor Trasylol in acute coronary occlusion in dogs In M Cantin G L Haberland G Schnells H Selye (eds) New aspects of Trasylol therapy 8: 381 Schattauer-Verlag Stuttgart-New York 1975

Sicuteri F Antonini F M DelBianco P L Franchi G Curradi C Pre kallikrein and kallikrein inhibitor in plasma of patients affected by recent myocardial infarction Adv Exp Med Biol 21 445 1972

Sicuteri F DelBianco P L Curradi C Monetti G The kinin system in cardiogenic shock In M Cantin G L Haberland G Schnells H Selye (eds) New aspects of Trasylol therapy 8 357 Schattauer-Verlag Stuttgart New York 1975

Sicuteri F Franchi G DelBianco P L DelBene E A contribution to the interpretation of shock and pain in myocardial infarction Malattie Cardiovasc 8 343 1967

Siegelman A M Carlsen A S Robertson T Investigation of serum trypsin and related substances I The quantitative demonstration of trypsin like activity in human blood serum by a micromethod Arch Biochem 97 159 1962

Sipilä R The plasma kinin system in acute pancreatitis Dissertation Helsinki 1977

Sipilä R Louhija A The application of bradykinin radioimmunoassay to plasma kininogen determination Biochem Pharmacol 25 543 1976

Sobel B E Bresnahan G F Shell W E Yoder R D Estimation of infarct size in man and its relation to prognosis Circulation 46 640 1972

Somer H Konttinen A Demonstration of creatine kinase isoenzymes by fluorescence technique Clin Chim Acta 40 133 1972

Staszewska Barczack J Ferreira S H Vane J R An excitatory nociseptive cardiac reflex elicted by bradykinin and potentiated by prostaglandins and myocardial ischemia Cardiovasc Res 10 314 1976

Staszewska Barczack J Vane J R The release of catecholamines from the adrenal medulla by peptides Brit J Pharmacol 30 655 1967

Streeten D H P Kerr L P Kerr C B Prior J C Dalakos T G Hyperbradykininism A new orthostatic syndrome Lancet 2 1048 1972

Talamo R C Haber E Austen K F A radioimmunoassay for bradykinin in plasma and synovial fluid J Lab Clin Med 74 816 1969

Terragno D A Crowshaw K Terragno N A McGiff J G Prostaglandin synthesis by bovine mesenteric arteries and veins Circ Res 36 37 (Suppl I) 1 1975

Trautschold I Assay methods in the kinin system In E G Erdös (ed) Handbook of experimental Pharmacology XXV 52 Springer-Verlag Berlin Heidelberg New York 1970

Uchida Y Kamisaka K Ueda H Developmental mechanism of anginal pain excitation dynamics of the cardiac sympathetic afferent nerve Jap Circ J 35 147 1971

Uchida Y Murao S Bradykinin induced excitation of afferent sympathetic nerve fibers Jap Heart J 15 84 1974

Uchida Y Ueda H Kininogen and kinin activity during local ischaemia in man Jap Heart J 10 503 1969

Ungar G Release of proteolytic enzyme in anaphylactic and peptone shock in vitro Lancet 1 708 1947

Willis A L Release of histamine kinin and prostaglandins during carrageenin induced inflammation in the rat In P Mantegazza E W Horton (eds) Prostaglandins Peptides and Amines Academic Press London 1969

Wong P Colman R W Talamo R C Babior B M Kallikrein bradykinin system in chronic alcoholic liver disease Ann Intern Med 77 205 1972

Wong P Y Talamo R C Babior B M Raymond C G Colman R W Kallikrein kinin system in postgastrectomy dumping syndrome Ann Intern Med 80 577 1974

Wuepper K D Prekallikrein deficiency in man J Exp Med 138 1345 1973

Wuepper K D Miller D R Lacombe M J Flaujeac trait Deficiency of kininogen in man Fed Proc 34 859 1975 (abstr)

Yang H Y T Erdös E G Second kininase in human plasma Nature 215 1402 1967

Yang H Y T Erdös E G Levin Y Characterization of a dipeptide hydrolase (kininase II angiotensin I converting enzyme) J Pharmacol Exp Ther 117 291 1971

Zacest R Mashford M L Blood bradykinin levels in the human Aust J Exp Biol Med Sci 45 89 1967

Zener J C Harrison D C Serum enzyme values following intramuscular administration of lidocaine Arch Intern Med 134 48 1974